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Non-motor symptoms in healthy Ashkenazi Jewish carriers of the G2019S mutation in the *LRRK2* gene

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Data analysis and interpretation was performed by Mirelman, Alcalay and Saunders-Pullman. Dr. Mirelman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She has also drafted the manuscript.

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Abstract

Background—The Asymptomatic carriers of the Leucine rich repeat kinase 2 (*LRRK2)* G2019S mutation represent a population at risk for developing PD. The aim of this study was to assess differences in non-motor symptoms between non-manifesting carriers and non-carriers of the G2019S mutation.

Methods—253 subjects participated in this observational cross sectional multi-center study. Standard questionnaires assessing anxiety, depression, cognition, smell, non-motor symptoms and REM sleep behavior were administered. Analyses were adjusted for age, gender, family relations, education and site.

Results—134 carriers were identified. carriers had higher non-motor symptoms score on the NMS questionnaire (p=0.02). These findings were amplified in carriers over the age of 50 with higher non-motor symptoms scores and trait anxiety scores (p<0.03).

Conclusions—In this cross section study, carriers of the G2019S *LRRK2* mutation endorsed subtle non-motor symptoms. Whether these are early features of PD will require a longitudinal study.

Keywords

Non-manifesting carriers; *LRRK2*; Parkinson's disease; prodromal

INTRODUCTION

Parkinson's disease (PD) has a long prodromal phase in which individuals may not complain of overt motor symptoms[1]. Pre-clinical motor and non-motor abnormalities likely develop gradually for many years before diagnosis[1]. The autosomal dominant G2019S mutation is associated with an increased frequency of PD in Ashkenazi Jews(AJ)[2], where rates approach as high as 26% in familial and 14% in sporadic PD[2;3]. However, penetrance is incomplete with age-specific estimates ranging from 15% at age 50–60 to 21–85% at age 70[2;4]. Recently we reported a lower than previously suggested penetrance of only 25% at age 80 in a kin-cohort analysis[5]. The asymptomatic carriers of the G2019S mutation represent a

population at risk for developing PD who may provide insight into the prodromal phase and development of PD.

Recent studies have shown differences between non-manifesting mutation carriers and non-carriers in smell identification[6], subtle gait changes, and aspects of executive function[7;8]. However, broad testing of non-motor symptoms in this cohort has not yet been reported. Based on the concept of pre-motor state, we hypothesized that differences in clinical features would be observed between these groups. Thus the aim of this study was to evaluate non-motor symptoms as obtained by standarized clinical measures in asymptomatic carriers and non-carriers of the G2019S mutation in the *LRRK2* gene.

METHODS

The study was conducted by the *LRRK2* AJ consortium which includes centers in Israel (Tel Aviv Medical Center; TLVMC) and New York (Beth Israel Medical Center; BI and Columbia University Medical Center; CU).

Participants

253 asymptomatic AJ relatives of PD patients, carriers of the G2019S *LRRK2* mutation participated in this double blind observational cross sectional study (BI=52, CU=49 and TLVMC=152). Exclusion criteria are available as supplementary material. The study was approved by the Institutional Review Boards at all sites. All participants signed consent prior to participation.

Clinical evaluation

Standarized clinical tests were used for the evaluation. Motor signs were quantified using the motor portion (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS)[9]. Non-motor symptoms and REM sleep behavior were assessed using the NMS and RBDQ questionnaires[10;11]. Cognitive assessment was performed using the Montreal Cognitive Assessment test (MoCA)[12] and validated neuropsychological tests (see supplemental material)[13;14]. Five cognitive domains: attention, memory, executive function, visuospatial function, and psychomotor speed, were created from transformed z-scores of the individual neuropsychological tests[15]. Depressive and anxiety symptoms were assessed using the abbreviated Geriatric Depression Scale (GDS-15)[16] and the Spielberg State and Trait Inventory (STAI)[17, 18] and the University of Pennsylvania Smell Identification Test (UPSIT) was used to assess olfaction[19;20].

Statistical Analysis

Neuropsychological test scores were transformed into z-scores using means and standard deviations[21]. Repeated measures (mixed model) ANCOVAs were used to compare continuous quantitative dependent variables between groups, and repeated measures (mixed model) logistic regression for similar binomial dependent variable. Regression models adjusted for gender and age. Family was used as the repeated (random) factor. SAS (SAS Institute, Cary, NC) MIXED procedure was employed for ANCOVAs, and the GENMOD procedure was used for logistic regression.

To explore potential prodromal signs, subjects were divided based on the median age of the cohort (50 years of age) for analysis of differences between "older" carriers and non-carriers. Comparison-wise p-values are presented in this exploratory study without adjustment for multiple comparisons, in order to avoid inflating type II errors.

RESULTS

134 carriers (mean age 49.5±16.8yrs; 44% males), and 119 non-carriers were enrolled (Table 1). No differences between groups were observed in age, gender, years of education or the UPDRS total or motor scores (p>0.58).

Performances on the cognitive tests were similar in the carriers and non-carriers after adjusting for education, gender, age and family (see Table 2).

No differences were observed in UPSIT scores between the groups (p=0.22). Carriers reported slightly more non-motor symptoms than non-carriers (p=0.02) reflecting a small effect size (cohen *d*= 0.46). More carriers reported constipation (question 5; p=0.01), and a sense of urinary urgency (question 8; p=0.02). RBDQ scores for both groups did not reflect RBD, but carriers reported slightly more sleep problems on the RBDQ (p=0.08; cohen *d*=0.27). Anxiety and depressive symptoms were within normal ranges, carriers demonstrated slightly higher trait anxiety than non-carriers (p=0.07) (see Table 2).

Subgroup analyses to assess the role of age

Sixty-seven carriers and 50 non-carriers were were considered the "older group" (mean age 64.8±11.7;48% males). Carriers and non-carriers in this group were similar in age, gender, years of education, scores on the cognitive tests (p>0.42) as well as on the UPDRS motor part III (carriers:4.2±3.1 vs. non-carriers:2.9±3.9; p=0.17).

Older carriers scored worse on the NMS questionnaire (carriers:3.7±2.9 vs. non-carriers: 2.3±2.1; p=0.03; cohen's *d*= 0.55) reporting more constipation, urinary urgency, daytime sleepiness and anxiety (questions 5,8,17,22) and had more trait anxiety than non-carriers (carriers:38.2±8.5 vs. non-carriers:34.1±5.9; p=0.03; cohen's *d*= 0.57). No differences were observed between carriers and non-carriers in the younger group.

DISCUSSION

Our study is the largest investigation of non-motor and motor features in an asymptomatic population of *LRRK2* G2019S carriers. Results indicate more non-motor symptoms as reflected by the NMS questionnaire in the carriers group than in non-carriers group. Differences between groups were more pronounced with older age. The analysis also found that older carriers presented increased anxiety as measured by the STAI questionnaire.

Previously, studies reported that an anxious personality trait may predict future development of PD, with trait anxiety more common among patients with PD[22;23]. These findings indicate a possible relationship between personality trait, disease risk and older age and strengthen the possibility that within this cohort there are asymptomatic individuals that may

develop overt symptoms of disease. This observation should be further explored in a longitudinal follow-up.

Contrary to our hypothesis, most measures were similar between the groups. Several explanations could be put forward to explain these findings. First, based on the reported low penetrance of *LRRK2*[5], it is possible that the present findings could be related to the endophenotype of the G2019S, with relatively few carriers eventually developing clinical PD, explaining the absence of marked prodromal signs. Thus a cross sectional assessment of carriers is expected to include both healthy carriers and subjects in different stages of the pre-motor disease and therefore differences between carriers and non-carriers are diluted.

Based on our previous studies[7;8;24], it could also be possible that while most carriers are affected by PD pathology, only few develop overt motor symptoms of PD due to adequate compensatory mechanisms. Thaler et al. reported differences in executive function between carriers and non-carriers using a comprehensive computerized program, but no differences were observed in standardized neuropsychological tests[8]. Similarly, carriers differed from non-carriers in sensitive gait measures during challenging walks that were used to impose a cognitive load and tax the compensatory mechanisms[7]. Both these studies used challenging testing conditions to overload the compensatory mechanisms and enable the detection of subtle changes in performance. Functional MRI studies performed on this cohort[24–26], using both motor and cognitive paradigms, identified between group differences in both task related activation and functional connectivity between cortical and basal ganglia structures[24–26] demonstrating neural changes that were not reflected clinically. These findings indicate that in order to identify early subtle changes in the prodromal phase, specific and sensitive assessment tools should be used. Further support to this idea comes from a recent review by Postuma et al[27] which suggested that specificity, and positive predictive value of non-motor features, such as the ones used in this study, may be insufficient to detect changes in prodromal disease.

Recently, Gaig et al[28] reported less NMS in PD *LRRK2* patients as compared to idiopathic PD with only 40% of patients presenting symptoms antedate to onset. This finding suggests that NMS in *LRRK2* PD may not be pronounced in the prodromal stage and may develop at a later stage of the disease. Non-motor symptoms have been reported to appear between 5 -10 years prior to the disease[29;30], thus the identification of prodromal signs is likely dependent on age. Our findings support this idea. Indeed in the present analyses, significant differences between the groups were mostly observed in the older age group with moderate effects size findings for both NMS and anxiety symptoms. Nevertheless, it is important to consider that groups were similar in age but the carriers demonstrated more NMS than the non-carriers, thus many of these individual differences are not solely dependent on age but also on genetic predisposition, environment, and compensatory mechanisms and may reflect prodromal signs.

Despite the minimal differences between the groups, we believe that the findings provide important insights. We suggest that more sensitive measures should be used to detect symptoms in the prodromal phase. In addition, it is likely that a single clinical symptom will not be sufficient to be considered as a sole biomarker for disease but rather that a cluster of

symptoms are likely to be more indicative however this will require confirmation in longitudinal studies. Such a study is now in progress in our cohort. Following this cohort will likely provide more information as to the intricate combination of symptoms that could better identify individuals at risk for developing PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Participant characteristics and motor scores. Median (Inter-Quartile Range)

	Carriers (n=134)	Non-Carriers (n=119)	P-value
Age (yrs)	49.5 (40–63.5)	47 (39–61)	0.33
Gender all (% male)	44.1%	49.6%	0.51
Year of education (yrs)	16 (14–18)	16 (15–18)	0.73
UPDRS total score	2 (1–5)	2 (0–5)	0.58
UPDRS Part III motor score	1 (0–4)	2 (0–3)	0.31
Cognitive Function			
MoCA	27 (25–29)	27 (24.5–28)	0.14
Attention (Z scores)	0.16 (−0.11–0.36)	0.03 (−0.18–0.31)	0.31
Memory (Z scores) $\mathcal{F}$	−0.35 (−0.44–0.70)	−0.59 (−0.61–0.25)	0.35
Executive function (Z scores)	0.18 (−0.16–0.55)	0.11(−0.1–0.58)	0.08
Visuospatial (Z scores) $\mathcal{F}$	0.72 (−0.87–0.37)	0.97 (−0.91–0.36)	0.42
Motor speed (Z scores)	−0.02 (−0.51–0.44)	0.01 (−0.43–0.37)	0.89
Non-motor symptoms			
UPSIT	34 (31–36)	33 (29–35)	0.22
NMS	3 (2–6)	2 (1–4)	0.02*
RBDQ	2(2–4)	1.5 (1–3)	0.08
STAI Trait	34 (25–44)	32 (27–37)	0.07
STAI State	32 (20–42)	29 (19–39)	0.42
Geriatric Depression Scale	1 (0–3)	1 (0–3)	0.48

UPDRS-Unified Parkinson's Disease Rating Scale, MoCA- Montreal Cognitive Assessment, Cognitive domains scores are presented in Z scores; the higher the score the better the performance, UPSIT- University of Pennsylvania Smell Identification Test, NMS- Non-Motor Symptoms Questionnaire, RBDQ-REM Sleep Behaviour Disorder Questionnaire, STAI- The Spielberg State and Trait Inventory.

$\mathcal{F}$ Test performed only in BI and CU.

* significant difference between groups.

Table 2

Mixed model analysis

	B	SE	95%Confidence interval	P-value
Motor function				
UPDRS motor part III	0.07	0.05	−0.02–0.02	0.12
Cognitive function				
MoCA	0.02	0.01	−0.01–0.05	0.18
Attention	0.07	0.08	−0.15–0.16	0.93
Memory $^{\mathcal{F}}$	−0.01	0.08	−0.17–0.15	0.87
Executive function	0.08	0.10	−0.13–0.28	0.46
Visualspatial $^{\mathcal{F}}$	−0.03	0.05	−0.13–0.83	0.62
Motor speed	0.24	0.06	−0.09–0.15	0.69
Autonomic function				
UPSIT	−0.48	0.29	−1.06–0.10	0.22
NMS	1.21	0.08	−0.53–1.09	0.02*
RBDQ	0.14	0.82	−3.05–0.16	0.09
STAI Trait	1.52	0.01	0.47–1.58	0.07
STAI State	1.47	0.02	0.37–2.81	0.42
Geriatric Depression Scale	0.65	0.44	−1.51–0.21	0.48

Models adjusted for age, gender and family. MoCA- Montreal Cognitive Assessment. Analysis adjusted for sex, age, years of education, site and pedigree. Cognitive domains scores are presented in Z scores. Scores on memory and visuospatial domains were available only from participants in NY. UPSIT- University of Pennsylvania Smell Identification Test, NMS- Non-Motor Symptoms, RBDQ- REM Sleep Behaviour Disorder Questionnaire, STAI- The Spielberg State and Trait Inventory.

$^{\mathcal{F}}$Test performed only in BI and CU.

*significant difference between groups.