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Cognitive and behavioral symptoms in Parkinson's disease patients with the G2019S and R1441G mutations of the LRRK2 gene

Johanne Hatteland Somme [b, *], Ana Molano Salazar [a], Amaia Gonzalez [a], Beatriz Tijero [a], Koldo Berganzo [a], Elena Lezcano [a], Manuel Fernandez Martinez [a], Juan Jose Zarranz [a], Juan Carlos Gómez-Esteban [a]

[a] Movement Disorders and Autonomic Unit, Department of Neurology, Cruces University Hospital, Department of Neurosciences, University of the Basque Country, Spain
[b] Department of Neurology, Alava University Hospital, Osakidetza, Spain

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ABSTRACT

Objective: To compare the cognitive and psychiatric status of patients with Parkinson's disease related to the G2019S and the R1441G mutations of the LRRK2 gene (LRRK2-PD) and idiopathic Parkinson's disease (iPD) patients.
Methods: We examined cognition and psychiatric symptoms in 27 patients with LRRK2-PD (12 G2019S and 15 R1441G) and 27 iPD patients.
Results: The groups were similar in age, education, disease duration, levodopa equivalent daily dose, and Unified Parkinson's Disease Rating Scale (UPDRS) II–IV; however, the LRRK2-PD showed less impairment on UPDRS-I (2.0 ± 1.7 vs. 4.2 ± 2.8, $p = 0.003$). The LRRK2-PD presented less frequent subjective cognitive complaints (18.5% vs. 63.0%, $p = 0.002$), and mild cognitive impairment or dementia (25.9% vs. 59.2%, $p = 0.027$). They also showed less impairment on scales for general cognition (Mattis dementia rating scale 131.2 ± 10.9 vs. 119 ± 24.0, $p = 0.022$), episodic verbal memory (Rey's auditory verbal learning test, immediate recall 39.2 ± 9.5 vs. 27.6 ± 12.8 $p < 0.001$, delayed recall 7.2 ± 3.7 vs. 4.7 ± 4.0 $p = 0.022$), and the Neuropsychiatric Inventory (9.7 ± 9.2 vs. 20.5 ± 14.3, $p = 0.004$, significant differences for apathy and hallucinations). The LRRK2-PD subjects were less frequently treated with antipsychotic medication (0% vs. 25.9%, $p = 0.010$). There were no significant differences between G2019S and R1441G mutation carriers.
Conclusions: Mutations of the LRRK2 gene might cause PD associated with less cognitive and neuropsychiatric impairment as compared to iPD.

1. Introduction

Mutations of the LRRK2 gene are the most common known cause of autosomal dominant hereditary Parkinson's disease (PD). The typical clinical syndrome is a late onset parkinsonism with a relatively benign disease course and good response to L-dopa. A total of seven different mutations have been linked to PD, the most common worldwide being the G2019S mutation [1]. However some ethnic groups show an especially high frequency of other mutations, as is the case of the R1441G in the Basque country in northern Spain [2].

Previous studies have indicated less or similar cognitive impairment in G2019S related PD when compared to idiopathic PD (iPD) patients [3,4]; however, some studies have indicated a possible higher prevalence of neuropsychiatric symptoms [5–7]. The published studies of PD related to mutations of the Ras of complex proteins GTPase domain of the LRRK2 gene (R1441 C/G/H) have reported clinical features similar to those of G2019S related and idiopathic PD [8–10]. Recently a detailed neuropsychological study of PD patients with the R1441G mutation was published showing no differences when compared to iPD subjects [11], even though a previous report had indicated a possible lower prevalence of dementia [12]. From a neuropathological point of view the

* Corresponding author. Department of Neurology, Alava University Hospital (Txagorritxu), C/ Jose Atxotegui s.n., 01009 Vitoria-Gasteiz, Alava, Spain. Tel.: +34 945007505.
E-mail address: johannehatteland.somme@osakidetza.net (J.H. Somme).

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G2019S mutation show diverse findings on autopsy; however, Lewy body pathology or abnormalities of alpha-synuclein solubility and aggregation is frequently found [13,14]. The only published autopsy study of the R1441G mutation reported neither Lewy pathology nor intracytoplasmic inclusions of alpha synuclein, tau, ubiquitin and LRRK2 [15]. This possible neuropathological difference between the two mutations could give rise to a difference in terms of cognition with R1441G showing less impairment.

The aim of this study was to compare cognition and behavioral symptoms in LRRK2 related PD (LRRK2-PD) and iPD, as well as between R1441G and G2019S mutation carriers. Our hypothesis, based on clinical experience and previous studies, was: that carriers of the LRRK2 mutation would show less cognitive impairment than iPD patients; and that R1441G mutation carriers present less impairment than G2019S mutation carriers.

2. Methods

Firstly we invited all patients with LRRK2-PD attending a movement disorders clinic in the Basque country in northern Spain to participate in the study. The mutation carriers had been identified through genetic testing of patients with PD with early age of onset or family history of PD. None of the patients declined to participate; however, two mutation carriers who had received neuropsychological testing with a different protocol due to intervention for deep brain stimulation of the subthalamic nucleus were excluded from the study. Demographic data of these patients were collected and subsequently iPD patients matched for age (±4 years), disease duration (±3 years) and education (±3 years) were recruited from the same movement disorders clinic. All controls were genetically tested to confirm absence of mutations of the LRRK2 gene.

3. Study protocol

Diagnosis of PD was made according to the UK Parkinson's disease society Brain Bank clinical diagnostic criteria (with exception of the family history exclusion criteria in the LRRK2 positive patients) [16]. The ethical committee approved the study; and all patients gave informed consent to participation before inclusion. Demographic data included received formal education expressed as number of years of full-time education. Clinical evaluation included a detailed neurological exam and the Unified Parkinson's Disease Rating Scale (UPDRS) I-IV in all patients. Information on dopamine replacement therapy was recorded; and levodopa equivalent daily dose (LEDD) was calculated according to the recommendations of Tomlinson et al. [17]. We also recorded use of psychotropic treatment divided in four main groups, antipsychotic, antidepressant, anxiolytic and hypnotic medication.

The neuropsychological study protocol was composed of two main parts; firstly a semi-structured interview with the patient and an informant, and secondly a battery of neuropsychological tests designed to assess a wide range of cognitive domains frequently impaired in PD. The interview assessed subjective cognitive complaints by direct questioning, and whether cognitive impairment significantly interfered with functional independence. Mattis dementia rating scale II (MDRS) [18] was used as a measure of general cognition with subscales for attention, memory, initiation-preservation, construction and conceptualization. Two further tests to assess memory were performed; Rey's auditory verbal learning test (RAVLT) assessing episodic verbal memory [19] (sum of learning trials or immediate recall, IR, and delayed recall, DR) and Benton visual retention test (BVRT) assessing visual memory [20]. The Stroop test was performed as a measure of processing speed, selective attention, and cognitive flexibility. Wechsler adult intelligence scale 3rd edition letter and number subscale (WAISIII-LN) was also performed as a measure of attention and working memory. To assess visuospatial function Benton judgment of line orientation test (BJLOT) [21], and the clock drawing test, with a max score of 10 [22], were used. Furthermore phonemic and semantic verbal fluency tests were performed; the former being more dependant on frontal function and the latter on temporal lobe function, the parietal lobe being important in both [23]. Phonemic verbal fluency was assessed using the letter “P” and semantic verbal fluency with the category “animals”, both with a time limit of 1 min. Raw scores were corrected for age, gender, and education according to available normative data. In all tests high scores is equal to better performance.

Some tests could not be performed in all individuals due to limitations of the individual patient, mainly illiteracy in the case of WAISIII-LN and severe visual impairment in the Stroop test and BJLOT, or due to the severity of the cognitive impairment. The missing scores have been imputed using the mean of the patient's group on scores missing due to illiteracy or visual problems, and the worst recorded score in the cases were the patient was too severely impaired to perform de test. The percentages of imputed data points in each test were: 3.7% for RAVLT, 1.9% for BVRT, 16.7% for STROOP, 20.4% for WAISIII-LN, and 24.1% for BJLOT. The remaining tests were performed in all individuals.

We used age, gender, and education corrected normative data for the different neuropsychological tests, as well as the information from the semi-structured interview to classify the patients into cognitively normal, PD with mild cognitive impairment (PD-MCI) and PD dementia (PD-D). Dementia was diagnosed according to criteria proposed by the Movement Disorders Society [24]. Non-demented individuals were further classified as cognitively normal or presenting mild cognitive impairment following the level I category guidelines of the Movement Disorders Society [25].

The presence of neuropsychiatric symptoms was assessed with the Neuropsychiatric Inventory applied to a caregiver with close contact with the patient [26].

4. Statistical analysis

Proportions were calculated for qualitative variables; and mean and standard deviation (SD) were calculated for quantitative variables. Means were compared with Student t-test and Mann–Whitney U test according to the distribution of the variables. Proportions were compared with the Fisher exact test. The low number of subjects inherent to all studies regarding these mutations might make it difficult to find any statistically significant differences especially when strict correction for multiple comparisons is applied. For this reason, to avoid inflation of type II errors, we chose not to correct for multiple comparisons [27].

5. Results

A total of 27 patients with LRRK2-PD (12 G2019S and 15 R1441G) and 27 patients with idiopathic PD (iPD) were included in the study. There were no significant differences in age, gender, disease duration, LEDD, and level of education between the three groups (Table 1). The UPDRS II, III, and IV did not show any significant differences between the groups in terms of motor experiences of daily living, motor examination, and motor complications; however, a significant difference was found in the non-motor experiences of daily living (UPDRS I) with the LRRK2 mutation carriers showing less impairment (Table 1).

In terms of subjective cognitive complaints there was a considerable difference between mutation carriers and iPD subjects: 17 (63.0%) of the latter presented complaints while only 5 (18.5%) of the LRRK2-PD patients (3 G2019S and 2 R1441G) did so ($p = 0.002$). Most subjective complaints were regarding deficits in memory or attention. There was also a significant difference in the total score of the global cognition scale (MDRS) between the LRRK2-PD and iPD subjects, with the latter showing a poorer