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# *LRRK2* G2019S mutation in Parkinson's disease: A neuropsychological and neuropsychiatric study in a large Algerian cohort☆

Soreya Belarbi [a], Nassima Hecham [a], Suzanne Lesage [b], Mohamed I. Kediha [a], Nourredine Smail [c], Traki Benhassine [d], Farida Ysmail-Dahlouk [a], Ebba Lohman [b], Badia Benhabyles [c], Tarik Hamadouche [e], Salima Assami [a], Alexis Brice [b], Meriem Tazir [a,*]

[a] *Laboratoire de Recherche en Neurosciences, Service de Neurologie, CHU Mustapha, Place du 1er Mai, Algiers 16000, Algeria*
[b] *INSERM UMR_S975 (formerly UMR_S679), Department of Genetics, Cytogenetics and Embryology, Pitié- Salpetrière Hospital, Paris, France*
[c] *Department of Epidemiology, CHU Mustapha, Algiers, Algeria*
[d] *Genetics Laboratory, FSB, Université Bab Ezzouar, Algiers, Algeria*
[e] *Molecular Biology Laboratory, Université M'hamed Bougara, Boumerdes, Algeria*

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ABSTRACT

A series of 106 patients with isolated or familial Parkinsonism underwent clinical evaluation and genetic testing for the *LRRK2* G2019S mutation which was identified in 34/106 patients (32%). Seventy one of them accepted to be evaluated for neuropsychological and neuropsychiatric studies with the aim to compare mutation carriers with non-carriers. For neuropsychological testing, comparisons between *LRRK2* G2019S carriers and non-carriers were made after stratification according to the level of education: median and high school versus low level. Memory was investigated with the five words test, 2 novel tests with verbalized visual material dedicated to illiterate patients, the TNI-93 (nine pictures test), The TMA-93 (associative memory test), and digit spans (forward/backward). Cognitive analyse did not show major differences between the two groups of patients. Nevertheless, behavioral abnormalities, mostly depression and hallucinations, were more frequent in the *LRRK2* G2019S carriers, suggesting the presence of a greater involvement of the limbic system in these patients. Sleep disorders which were also more common amongst mutation carriers than non-carriers might be related to depression.


## 1. Introduction

Idiopathic Parkinson's disease (PD) is the second most frequent neurodegenerative disorder in the elderly and the most common movement disorder. Although the cause of PD remains unclear, its etiology is most likely a combination of complex genetic and environmental factors [1]. Approximately 85% of cases were sporadic, with familial clustering seen in 10–15% and monogenic inheritance in less than 10% [2]. There are at least 13 known loci, with 9 causative genes identified to date [3]. The recent discovery of the *LRRK2* (Leucine-rich repeat kinase 2) gene that encodes dardarin, revolutionized the genetics of Parkinson's disease, since a single G2019S mutation causes a significant proportion of autosomal dominant forms of PD. Thus, it represents the most common mutation identified in PD so far. Subsequent studies have shown that the frequency of *LRRK2* G2019S mutation varies greatly according to geographical or ethnic origin. The highest frequency was found in North African Arabs where this mutation accounts for 41% of isolated and 37% of familial PD [4], versus 1–2% and 5–6% in Europe [5]. Furthermore, the G2019S mutation was found in approximately 30% of Ashkenazi Jews with familial forms of PD, and 13% of cases with no family history of PD [6]. Recently, we reported a clinical and genetic study of a series of 136 PD patients from North Africa and confirmed the high proportion of *LRRK2* G2019S mutation among these patients [7]. In this study, a comparison of the clinical features of PD between G2019S mutation carriers and non-carriers revealed that they were similar except for L-Dopa induced dyskinesias which were significantly more frequent in the group with G2019S mutation (53%) than without (16%). Non-motor symptoms were not studied in this subset of PD patients. In order to achieve a full clinical characterization of PD patients harboring this mutation and to compare them with non-carriers, we decided to undertake detailed neurological but especially a neuropsychological and psychiatric evaluation of 106 patients from this series.

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* Corresponding author. Tel./fax: +213 21 23 56 40.
*E-mail address:* meriem.tazir@sante.dz (M. Tazir).

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## 2. Methods

A series of 106 patients with isolated or familial parkinsonism, consecutively ascertained in our movement disorders out patients clinic at the Mustapha Bacha hospital (Algiers, Algeria), underwent clinical evaluation and genetic testing for the *LRRK2* G2019S mutation [7]. The G2019S mutation was identified in 34/106 patients (32%). All these patients were called in for neuropsychological and neuropsychiatric evaluations. Seventy one of them accepted and gave informed consent to take part in this study which was approved by the local Ethics committee.

### 2.1. Neuropsychological and neuropsychiatric evaluations

The neuropsychological battery included the mini-mental state examination (MMSE) and the Mattis Dementia Rating Scale (MDRS) which were used to assess global intellectual efficiency. MMSE normal values were used according to the standards of the PAQUID study [8]. For patients with median and high educational level, low MMSE values were below 24, whereas for patients with low educational level, values below 19 were considered as low.

*Memory* was investigated with the five words test, the TNI-93 (nine pictures test), the TMA-93 (associative memory test), and digit spans (forward/backward). TNI and TMA are 2 novel tests with verbalized visual material, dedicated to illiterate patients [9]. TMA is a spot of associative learning in which the subject is asked to call and check out 3 cued recalls of 10 pairs of semantically related pictures. The TNI which is derived from the MIS (Memory Impairment Screen) [10] consists of the name and learning of a series of 9 verbalized pictures. After an interferential phase, patients are subjected to a spot of free and cued recall.

### 2.2. Executive functions

They were assessed with verbal fluencies (phonemic-PF and category fluencies-CF), the trail making test (part A/B), the frontal assessment battery (FAB), Isaac's test, the Stroop Color-Word Test and clock drawing task (CDT). Owing to a high prevalence of illiteracy among patients, the neuropsychological battery used took into account the level of education, with one battery for the low level (without any school education) and another for the median and high level (with at least the primary school certificate).

### 2.3. Neuropsychiatric status and behavior

They were evaluated with the neuropsychiatric inventory (NPI). Depression was diagnosed and evaluated using the criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM IV), the Hamilton Depression Rating Scale (HDRS) and the Montgomery Asberg Depression Rating Scale (MADRS).

Statistical analyses included qualitative and quantitative comparisons of demographic and clinical characteristics between mutation carriers and non-carriers and were computed using chi-square and *t*-test. Logistic regression was performed in the multivariate analysis. The relative risk was estimated through calculations of odds ratios (OR) with 95% confidence intervals (CI).

## 3. Results

Of the 71 patients (45 men, 26 women) who underwent cognitive and neuropsychiatric testing, 23 (11 men, 12 women) were G2019S mutation carrier and 48 (34 men, 14 women) non-carriers. The two groups of patients had similar age at onset and age at examination.

### 3.1. Neuropsychological assessment

Comparison between *LRRK2* G2019S carriers and non-carriers were made after stratification according to the level of education (median and high school versus low level). Neuropsychological examination of 22 patients with median or high level of education who had similar age at onset, age at examination and disease duration, did not reveal major differences in general cognitive efficiency (MMSE, MDRS) between *LRRK2* G2019S carriers and non-carriers (Table 1). Memory evaluation did not reveal a significant difference in working memory (digit spans) and episodic memory (the five word test) among the two groups. Executive function abnormalities were not significant between *LRRK2* G2019S carriers and non-carriers. Overall, frontal lobe deficits (as shown by FAB scores) were found in 43% of carriers and 40% of non-carriers (Table 1). Analysis of executive functions showed a deficit particularly affecting the verbal fluency and trail making test in both groups. The loss of inhibitory control was more frequent among the non-carrier patients (80% versus 43%), but the difference was not statistically significant.

**Table 1**
Cognitive assessment of PD patients with and without *LRRK2* G2019S mutation. Median and high level of education.

| | G2019S carriers $N = 7$ | | G2019S non-carriers $N = 15$ | |
|---|---|---|---|---|
| Sex ratio (Men: Women) | 5:2 | 7 | 14:1 | 15 |
| Mean age at examination (years) | 62.86 ± 9.70 | 7 | 66.47 ± 4.70 | 15 |
| Mean age at onset (years) | 52.14 ± 7.22 | 7 | 57.07 ± 5.38 | 15 |
| Disease duration (years) | 10.71 ± 3.84 | 7 | 9.40 ± 2.91 | 15 |
| Impairment% | | | | |
| MMSE | 14 | 7 | 6.7 | 15 |
| MDRS | 66.7 | 6 | 28.6 | 14 |
| Attention | 16.7 | 6 | 7 | 14 |
| Initiation | 33 | 6 | 28.6 | 14 |
| Construction | 16.7 | | 7 | 14 |
| Conceptualization | 16.7 | 6 | 7 | 14 |
| Memory | 16.7 | 6 | 7 | 14 |
| Digit spans | | | | |
| Forward | 42.9 | 7 | 40 | 15 |
| Backward | 28.6 | 7 | 33 | 15 |
| The five word test | 14.3 | 7 | 7 | 14 |
| FAB | 42.9 | 7 | 40 | 15 |
| Similarities | 42.9 | 7 | 20 | 15 |
| Lexical fluency | 28.6 | 7 | 40 | 15 |
| Motor series | 14.3 | 7 | 0 | 15 |
| Conflicting instructions | 14.3 | 7 | 13 | 15 |
| Go-No-Go | 42.9 | 7 | 80 | 15 |
| Phonemic fluencies | 80 | 5 | 58 | 12 |
| Category fluencies | 80 | 5 | 75 | 12 |
| Trail making test | | | | |
| Part A | 60 | 5 | 38 | 13 |
| Part B | 60 | 5 | 30.8 | 13 |
| Clock drawing task | 14 | 7 | 14 | 14 |
| Stroop color-word test (interference) | 16.7 | 6 | 38.5 | 13 |

MMSE: Normal values according to the standards of the PAQUID study.
MDRS: values <130 were considered pathological.
Forward digit span: values <5 were considered pathological.
Backward digit span: values <3 were considered pathological.
The five word test: values <8 were considered pathological.
FAB: values<13 were considered pathological.
Phonemic fluencies: values <16 were considered pathological.
Category fluencies: values <24 were considered pathological.
The trail making test: Normal values according to Allain Ph. et al. study [16].
CDT: values <2 were considered pathological.

Forty-nine patients with low educational level were assessed for their cognitive status. Age at onset and age at examination were similar in *LRRK2* G2019S carriers and non-carriers but not disease duration which was longer in the former (Table 2). Low MMSE values were more frequent in carriers (56%) than non-carriers (27%, $p = 0.04$). As the low MMSE values could reflect longer disease duration in the G2019S carriers, MMSE was analyzed as a dependent variable in multiple logistic regression models, using genetic status, age at onset, gender and disease duration, as covariates. According to the model, the G2019S mutation did not have a significant role in the impairment of MMSE after correction for these factors, this difference being explained by a longer disease duration compared with non-carriers ($p = 0.04$). We did not find major differences in executive functions and memory evaluations between the 2 groups of patients (Table 2).