123I-MIBG cardiac uptake and smell identification in parkinsonian patients with LRRK2 mutations

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Abstract Reduced uptake of 123I-metaiodobenzylguanidine (MIBG) on cardiac gammagrapy and impaired odor identification are markers of neurodegenerative diseases with Lewy bodies (LB) as a pathological hallmark, such as idiopathic Parkinson’s disease (IPD). LRRK2 patients present with a clinical syndrome indistinguishable from IPD, but LB have not been found in some cases. Patients with such mutations could behave differently than patients with IPD with respect to MIBG cardiac uptake and olfaction. We studied 14 LRRK2 patients, 14 IPD patients matched by age, gender, disease duration and severity, and 13 age and gender matched control subjects. Olfaction was analyzed through the University of Pennsylvania Smell Identification Test (UPSIT). MIBG cardiac uptake was evaluated through the \( H/M \) ratio. The late \( H/M \) was 1.44 ± 0.31 for LRRK2 patients, 1.19 ± 0.15 for PD patients, and 1.67 ± 0.16 for control subjects. LRRK2 patients presented lower but not statistically significant MIBG cardiac uptake than controls (\( p = 0.08 \)) and significant higher uptake than PD patients (\( p = 0.04 \)). UPSIT mean scores were 21.5 ± 7.3 for LRRK2 patients, 18.7 ± 6.2 for IPD patients and 29.7 ± 5.7 for control subjects. UPSIT score was lower in both LRRK2 and PD than in controls. In LRRK2 patients a positive correlation was found between myocardial MIBG uptake and UPSIT scores, (\( R = 0.801, p < 0.001 \)). In LRRK2 patients, MIBG cardiac uptake was less impaired than in PD; a positive correlation between MIBG cardiac uptake and UPSIT scores was observed. As MIBG cardiac reduced uptake and impaired odor identification are markers of LB pathology, this findings may represent neuropathological heterogeneity among LRRK2 patients.

Keywords Genetics · Lewy bodies · Parkinson’s disease · Smell · SPECT

Introduction

The clinical picture of patients with parkinsonism carrying LRRK2 gene mutations (LRRK2) is indistinguishable from that of Parkinson’s disease (PD) [1–3]. Postmortem descriptions of these patients indicate that the pathological substrate is heterogeneous with Lewy bodies (LB) in some cases, and with tau-immunopositive neurofibrillary tangle pathology, nigral degeneration with ubiquitin immunoreactive neuronal inclusions or pure nigral cell loss, in some others [1–9].

123I-MIBG cardiac scintigraphy (MIBG) reflects presynaptic sympathetic system integrity, and reduced myocardial uptake of this tracer suggests cardiac sympathetic denervation. Pathologic studies have demonstrated the presence of LB pathology and degeneration of the distal axons in the sympathetic ganglia and nerves of the cardiac plexus from patients with PD and dementia with LB [10], indicating that LB pathology itself might cause cardiac sympathetic denervation and low MIBG uptake [11]. Since MIBG cardiac uptake is normal in other parkinsonian syndromes in which LB are absent [12, 13], reduced uptake...
of this tracer has been proposed as a marker for those neurodegenerative disorders related to LB pathology.

Impaired odor detection has been also suggested as a potential marker for those disorders with an underlying LB pathology and to differentiate PD from other parkinsonian syndromes [14–17]. Since the presence of LB in LRRK2 is inconstant, and both MIBG reduced cardiac uptake and impaired odor identification, are proposed markers for the presence of LB pathology, patients with such mutations could behave differently than patients with IPD with respect to cardiac denervation and olfaction.

This is a prospective study to investigate the MIBG cardiac uptake and smell function in patients with PD carrying LRRK2 mutations.

**Methods**

**Design**

This was a prospective parallel group to study the MIBG cardiac uptake and smell function in patients with PD carrying LRRK2 mutations. The study protocol was approved by the local ethics committee. All patients signed an informed consent before entering the study.

**Subjects of the study**

Fourteen patients with parkinsonism carrying previously identified pathogenic mutations of the LRRK2 gene (LRRK2) were enrolled in the study. Of these patients, 13 presented the LRRK2 G2019S mutation and one, the R1441G mutation. Only two out of the 14 patients were relatives (mother and son). LRRK2 mutations were identified as previously described [3, 8]. We also included 14 PD patients diagnosed according to accepted clinical criteria [18] that were matched in age, gender, disease duration, and severity to patients with LRRK2 mutations. All PD patients were studied for the possible existence of the LRRK2 G2019S and codon 1441 mutations which were ruled out in all of them. We also included 13 age and gender matched control subjects without any neurological disorder that were selected among spouses of the PD and LRRK2 patients.

Exclusion criteria for entering the study were the same for all three groups of subjects and were mainly determined by those circumstances that could potentially modify MIBG cardiac uptake or smell function: (a) previous history of diabetes mellitus, peripheral neuropathy, cardiopathy or coronaryopathy; (b) patients receiving any medication known to modify the MIBG uptake such as tricyclic antidepressants, MAO inhibitors, calcium antagonists, neuroleptics and sympathomimetics and adrenergic drugs [19] (dopaminergic drugs were not discontinued since they are not among the drugs known to interfere with MIBG uptake); (c) proven iodine allergy; (d) patients with previous (such as significant cranial traumatism) or current (such as having a cold or tobacco consumption) conditions or rhinologic disorders known to impair the sense of smell [20]; (e) dementia or significant cognitive impairment (Mini-Mental State Examination score < 25) that could impair (or interfere with) odor identification.

Clinical assessment

After collection of detailed aspects of their clinical history, all IPD and LRRK2 patients were assessed through the Unified Parkinson’s Disease Rating Scale (UPDRS), Schwab & England scale and Hoehn & Yahr staging system at the first visit when entering the study after the usual morning dose of antiparkinsonian medication. Antiparkinsonian and other pharmacological treatments were recorded and levodopa equivalent daily dose was calculated.

**Olfaction testing**

Olfaction was evaluated through the University of Pennsylvania Smell Identification Test (UPSIT), commercially known as the Smell Identification Test™ (Sensonics, Spanish version) during the same day when MIBG cardiac scintigraphy was performed. The UPSIT is a rapid and easy-to-administer method to quantitatively assess human olfactory function, and includes 40 odors that should be identified. Scores range from 0 to 40 and higher scores entail a better olfactory recognition or function.

**MIBG cardiac gammagraphy**

Following thyroid gland blocking with potassium iodide (300 mg), anterior planar images of the chest were obtained and data were collected for 30 min, and 4 h after injection of 111 MBq of MIBG a static image was obtained with a 128 × 128 matrix using a double-head gamma camera system (Siemens E-CAM Dual-head, Erlangen, Germany). The organ uptake of MIBG was determined by setting the regions of interest (ROI), which were manually drawn around the left cardiac ventricle, and the upper mediastinum. The average counts per pixel in the heart and mediastinum were determined within each region of interest to calculate the heart-to-mediastinum (H/M) ratio at 30 min (early ratio) and 4 h (late ratio).

**Statistical analyses**

Since many variables were not normally distributed, as pointed out by the Kolmogorov–Smirnov test, non-parametric tests were used to assess differences between
groups. The Kruskal–Wallis analysis and the Mann–Whitney U test were used to compare the means of groups for multiple comparisons and in pairs, respectively. To determine whether there was a relationship among MIBG ratios and UPSIT score or other variables such as age, gender, disease duration, and Hoehn & Yahr stage in any group of subjects, Spearman correlation coefficient was obtained. A significance level of <0.05 was used. The statistical analyses were performed using commercially available software (SPSS, Version 17.0).

Results

The main demographic and clinical data of the subjects included in this study are summarized in Table 1. The results of the early and late H/M ratios obtained through the cardiac MIBG gammagrapy study are shown in the Table 2. The mean early H/M ratio in LRRK2 patients was significantly higher than in PD (p = 0.02) and slightly lower than in controls (p = 0.06). The mean early H/M ratio in the PD group was significantly lower than in controls (p < 0.01).

The mean late H/M ratio in LRRK2 patients was not significantly lower than in controls (p = 0.08), but was significantly different than in PD patients (p = 0.04). The late H/M ratio in PD patients was significantly lower than in controls (p < 0.01). There was not any significant overlap between late H/M ratios values in PD patients and those found in control subjects. By contrast, the late H/M ratios of LRRK2 patients presented a greater dispersion of values, which were intermediate between PD and control subjects (Fig. 1).

The mean UPSIT scores are also shown in Table 1. LRRK2 patients presented slightly greater scores than PD patients, but this difference was not statistically significant (p = 0.31), and both LRRK2 patients and PD showed significantly lower scores than controls (p < 0.01 and p < 0.01, respectively).

In LRRK2 patients a positive correlation was found between both MIBG early or late H/M ratios and the UPSIT score (for early H/M ratio: R = 0.72, p = 0.004; and for delayed H/M ratio: R = 0.71, p = 0.006). These correlations are shown in Fig. 2. Both PD patients and control subjects did not show any correlation between early or late H/M ratios and UPSIT scores (in PD patients, for early H/M ratio: R = 0.49, p = 0.08; and for delayed H/M ratio: R = 0.32, p = 0.26; in controls, for early H/M ratio: R = 0.29, p = 0.34; and for delayed H/M ratio: R = −0.11, p = 0.71). Most of the LRRK2 patients showing altered MIBG ratio where those presenting abnormal UPSIT scores, while all LRRK2 patients with normal MIBG ratio also had normal UPSIT scores (Fig. 3). There were no statistical differences in any demographic or clinical data in LRRK2 patients with normal MIBG uptake compared with those presenting reduced MIBG uptake (Table 3).

We did not find any correlation between either early or late H/M ratios and other clinical variables such as age, gender, disease duration, and Hoehn & Yahr stage in any group of subjects, but a non significant trend was observed between disease duration and H/M ratios in

| Table 1 Demographic and clinical data of the subjects of the study |
|---------------------------------------------------------------|
| **IPD** (n = 14) | **LRRK2** (n = 14) | **Controls** (n = 13) | **p** |
| Sex (male/female) | 8/6 | 8/6 | 7/6 | 0.89\(^a\) |
| Age (years), mean ± SD (range) | 62.1 ± 11.6 (45–85) | 61.9 ± 12.6 (43–92) | 63.5 ± 11.9 (45–85) | 0.95\(^b\) |
| Smokers | 1 | 3 | 2 | 0.54\(^b\) |
| Age at PD diagnosis (years), mean ± SD (range) | 52.1 ± 12.6 (36–81) | 52.1 ± 14.3 (33–86) | – | 0.35\(^b\) |
| Duration from PD diagnosis (years), mean ± SD (range) | 9.9 ± 4.2 (4–18) | 9.8 ± 5.9 (4–28) | – | 0.51\(^b\) |
| UPDRS part II (On) score, mean ± SD (range) | 6.6 ± 4.4 (0–14) | 11.1 ± 8.6 (1–26) | – | 0.87\(^b\) |
| UPDRS part III (On) score, mean ± SD (range) | 15.6 ± 9.1 (2–38) | 20.3 ± 13.5 (8–48) | – | 0.80\(^b\) |
| UPDRS part IV score, mean ± SD (range) | 3.6 ± 3.5 (0–10) | 3.7 ± 3.3 (0–10) | – | 0.15\(^b\) |
| Schwab & England (On) Scale, mean ± SD (range) | 90.0 ± 7.8 (70–100) | 87.9 ± 11.2 (70–100) | – | 0.60\(^b\) |
| Hoehn & Yahr (On) stage, mean ± SD (range) | 1.7 ± 0.7 (1–3) | 1.9 ± 0.7 (1–3) | – | 0.35\(^b\) |
| Levodopa equivalent daily dose (milligrams), mean ± SD (range) | 1,145.1 ± 441.4 (300–1,735) | 921.0 ± 350.2 (285–1,434) | – | 0.15\(^b\) |

\(^a\) Kruskal–Wallis analysis

\(^b\) Mann–Whitney U test
Table 2 Early and late myocardial \(^{123}\)I-MIBG H/M ratios and UPSIT scores obtained in LRRK2, IPD patients, and healthy matched control subjects

|               | LRRK2          | IPD            | Controls       | p           |
|---------------|----------------|----------------|----------------|-------------|
| Early H/M ratio | 1.49 ± 0.24 (1.09–1.82) | 1.31 ± 0.14 (1.13–1.64) | 1.66 ± 0.13 (1.39–1.87) | 0.02*       |
| Late H/M ratio  | 1.44 ± 0.31 (0.96–1.94) | 1.19 ± 0.15 (1.04–1.59) | 1.67 ± 0.16 (1.30–1.90) | 0.04*       |
| UPSIT score    | 21.5 ± 7.3 (8–31) | 18.7 ± 6.2 (9–32) | 29.7 ± 5.7 (19–38) | 0.31*       |

Numbers are the mean and standard deviation. The range appear in brackets
* Mann–Whitney U test: p value for LRRK2 versus IPD comparison
§ Mann–Whitney U test: p value for LRRK2 versus control subjects comparison
+ Mann–Whitney U test: p value for IPD versus control subjects comparison

Fig. 1 Scatter plot showing early (a) and late (b) H/M ratios for \(^{123}\)I-MIBG cardiac uptake in patients with idiopathic Parkinson’s disease (IPD), patients with parkinsonism and LRRK2 mutations (LRRK2-PD) and controls. Circles represent individual values; the bar refers to the mean H/M ratio in each group.

Fig. 2 Relationship between early (a) and delayed (b) H/M ratio for \(^{123}\)I-MIBG cardiac uptake and UPSIT scores in patients with parkinsonism and LRRK2 mutations. (Early: \(R = 0.62\) p < 0.02; late: \(R = 0.68\) p = 0.01)
Discussion

The cardiac uptake of MIBG was significantly less impaired in LRRK2 than in PD patients. In LRRK2 patients, abnormalities in smell function correlated with MIBG cardiac uptake impairment.

These findings are in agreement with a previous study showing normal MIBG myocardial uptake in three out of six patients carrying the LRRK2 G2019S mutation [21], and in most patients with I2020T or G2019S [22]. In the present study, olfactory function was not significantly different in LRRK2 patients and PD patients, a similar finding that was previously shown in another study in parkinsonian patients carriers of the G2019S mutation in which UPSIT scores were lower than that in healthy controls and similar to that found in patients with PD [23].

Similar studies have been conducted in patients with parkin mutations [22, 24, 25]. In most of these patients the cardiac uptake of MIBG was found to be normal. Post-mortem studies of some of these patients revealed the preservation of cardiac sympathetic nerves [24]. In addition, olfactory function in patients carrying parkin mutations has been shown to be similar to healthy controls and better than those observed in PD cases [26]. The most frequent neuropathological substrate in patients with parkinsonism related to parkin mutations is nigral degeneration without distinctive pathological inclusions [27, 28]. The differences in myocardial MIBG uptake and olfactory function between parkin and PD patients is probably reflecting the preservation of cardiac sympathetic plexus and olfactory anatomical structures in parkin patients, and lend support to the notion that both hyposmia and abnormal myocardial MIBG scintigraphy are indicators of LB pathology.

In this context, the cardiac gammagraphy findings of the present study may reflect that the presence of LB in LRRK2 patients is inconstant, variable, or that LB are present in fewer amounts. To date, the neuropathology associated with the LRRK2 G2019S mutation has been described in 21 cases with a clinical picture of progressive parkinsonism [2, 4–9, 21, 29]. In 18 of these cases, typical LB pathology was present, non-specific nigral degeneration similar to that described in patients with parkin gene

Table 3 Summary of the demographic data, disease features and UPSIT score in LRRK2 patients with normal MIBG uptake compared to LRRK2 patients with reduced MIBG uptake (cut-off for abnormal delayed H/M ratio = 1.43)

|                          | LRRK2 patients with normal delayed H/M ratio (n = 5) | LRRK2 patients with reduced delayed H/M ratio (n = 9) | p     |
|--------------------------|----------------------------------------------------|-----------------------------------------------------|-------|
| Sex (female, %)          | 3 (60%)                                            | 3 (33.3%)                                           | 0.58  |
| Age (years), mean ± SD (range) | 67.4 ± 17.6 (43–92) | 58.9 ± 8.3 (49–70)                                  | 0.44  |
| Age at PD diagnosis (years), mean ± SD (range)         | 60.2 ± 19.6 (33–86) | 47.7 ± 8.9 (35–64)                                  | 0.19  |
| Duration from PD diagnosis (years), mean ± SD (range) | 7.2 ± 2.7 (4–10)    | 11.2 ± 6.9 (6–28)                                   | 0.15  |
| UPDRS part II (ON) score, mean ± SD (range)          | 12.6 ± 11.0 (3–26)  | 10.33 ± 7.6 (1–23)                                  | 0.8   |
| UPDRS part III (ON) score, mean ± SD (range)         | 20.8 ± 16.7 (9–48)  | 20.0 ± 12.4 (8–42)                                  | 1.0   |
| UPDRS part IV score, mean ± SD (range)               | 2.6 ± 3.8 (0–9)     | 4.3 ± 3.0 (0–10)                                    | 0.24  |
| Schwab & England (On) Scale, mean ± SD (range)       | 90.0 ± 12.2 (70–100) | 86.7 ± 11.2 (70–100)                                | 0.61  |
| Hoehn & Yahr (On) stage, mean ± SD (range)           | 1.8 ± 0.4 (1–2)     | 1.9 ± 0.8 (1–3)                                     | 0.9   |
| Levodopa equivalent daily dose (LED) (milligrams), mean ± SD (range) | 642.0 ± 341.2 (285–1,010) | 1,076.0 ± 255.7 (705–1,434) | 0.29  |
| UPSIT Score, mean ± SD (range)                        | 28.4 ± 2.6 (25–31)  | 17.8 ± 6.1 (8–25)                                   | <0.01*|

* Statistically significant: p < 0.05
mutations occurred in two, and tau-immunopositive neurofibrillary tangle pathology in one case. Thus, the most frequent histological findings encountered in parkinsonism with LRRK2 G2019S mutation is LB pathology, although up to 14% of the cases can present another pathological substrate without the presence of LB and Lewy neurites. The neuropathological findings associated with LRRK2 R1441G mutations are nigral cell loss without distinctive pathological inclusions, described so far in a single case [9]. In the single patient of the present series carrying the R1441G mutation, a severe hyposmia and marked low MIBG uptake was found suggesting the presence of underlying LB pathology in this case.

A strong positive correlation between UPSIT scores and MIBG uptake was found in LRRK2 patients. This fact enhances the idea of a close association between cardiac uptake of MIBG and olfactory function. Reduced uptake of MIBG and reduced smell sense are usually decreased in PD patients, even in patients with a recent diagnosis of the disease, suggesting an early involvement by the pathological process associated to LB of both, the cardiac sympathetic nerve and olfactory bulb [30–34]. Some studies have found that MIBG uptake correlate with olfactory function in PD patients [35], a correlation that is not found in multiple system atrophy [36]. In addition, a recent study have shown that smell loss is associated with baroreflex failure and cardiac noradrenergic denervation in PD patients [37]. All these observations may indicate that cardiac sympathetic nervous system degenerates in parallel with the olfactory system. In our study, smell function was not significantly different in LRRK2 than in PD patients, although it was slightly better and there was a statistical trend. This fact probably reflects that smell function can be influenced by many independent factors while MIBG cardiac uptake is more specific of the presence of LB pathology.

In our study, the disease duration and severity was not correlated with either the MIBG uptake parameters or with UPSIT scores. LRRK2 patients with abnormal MIBG scans had younger age of onset, longer disease duration and higher L-dopa doses than the LRRK2 patients with normal MIBG scans, but none of these differences reached statistical significance. In our opinion, the differences in disease duration and age at onset could hardly explain differences in MIBG. LRRK2 patients with normal MIBG also had normal UPSIT score (in the range of controls), in contrast to those with abnormal MIBG who had abnormal UPSIT scores (in the range of IPD), suggesting that normal MIBG likely reflect absence of LB pathology. The possible association of MIBG uptake with the severity and duration of the disease is controversial. Different studies have shown that the disease severity is not correlated [38] or can be correlated [39, 40] with MIBG myocardial uptake. It has been suggested that degeneration of the cardiac sympathetic nerves and the olfactory bulb nerve occurs early in the disease process, even before the onset of degeneration at the nigral level [11]. This fact may account for the decreased cardiac uptake of MIBG and smell loss at the beginning of the disease and could explain the lack of correlation of MIBG myocardial uptake and the clinical markers of disease progression.

In conclusion, MIBG cardiac uptake in parkinsonian patients with LRRK2 mutations is abnormal but less impaired than in IPD, a finding that might be attributed to neuropathological heterogeneity among LRRK2 patients. MIBG reduced uptake is correlated with worse olfactory function in LRRK2 PD patients, supporting the notion that both abnormalities can be specific markers for the presence of LB in patients with LRRK2 mutations. It would be of great interest to follow-up these patients and make serial MIBG in order to observe the possible changes taking place after disease progression. The hypothesis stated in this study can be confirmed only through post-mortem analyses of the LRRK2 brains. Most of LRRK2 patients enrolled in the study accepted brain donation.

Conflict of interest None.

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