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Quitting smoking: An early non-motor feature of Parkinson's disease?

Marcello Moccia [a], Roberto Erro [b, c], Marina Picillo [d], Edoardo Vassallo [d], Carmine Vitale [e, f], Katia Longo [e], Marianna Amboni [e], Gabriella Santangelo [g], Raffaele Palladino [h, i], Antonio Nardone [i], Maria Triassi [i], Paolo Barone [d, *], Maria Teresa Pellecchia [d]

[a] Department of Neuroscience, Reproductive Science and Odontostomatology, Federico II University, Naples, Italy
[b] Sobell Department of Motor Neuroscience and Movement Disorders, University College London (UCL) Institute of Neurology, London, United Kingdom
[c] Department of Neurological and Movement Sciences, University of Verona, Policlinico Borgo Roma, Verona, Italy
[d] Center for Neurodegenerative Diseases (CEMAND), Neuroscience Section, Department of Medicine, University of Salerno, 84131, Italy
[e] IDC Hermitage Capodimonte, Naples, Italy
[f] Department of Motor Sciences, University Parthenope, Naples, Italy
[g] Neuropsychology Laboratory, Department of Psychology, Second University of Naples, Caserta, Italy
[h] Department of Primary Care and Public Health, Imperial College, London, United Kingdom
[i] Department of Public Health, Federico II University, Naples, Italy

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ABSTRACT

Introduction: Epidemiological studies report a 60–70% reduced risk of Parkinson's disease (PD) in smokers as compared to non-smokers. However, relationships between former smoking and PD have been poorly investigated.
Methods: We recruited 116 de novo PD subjects, and investigated current, former and never smoking, and reasons for smoking cessation among former smokers. Two hundred and thirty-two controls were matched by Propensity Score.
Results: PD subjects and controls were found to be current smokers (7.7 vs. 39.6%), former smokers (43.9 vs. 6.5%) and never smokers (48.2 vs. 53.9%). Logistic regression showed that current smokers were less likely to have PD ($p < 0.001$; OR: 0.22; 95% CI: 0.10–0.46), while former smokers were more likely to have PD ($p < 0.001$; OR: 7.6; 95% CI: 4.09–15.75), as compared to never smokers. Fifty-one PD patients reported quitting smoking before PD diagnosis (mean time since cessation 9.4 ± 7.3 years). Most important reasons to quit smoking in PD group were illness different from PD (26 subjects, 51.0%), knowledge of the harmful effects of smoking (24 subjects, 47.0%), and physician's advice (1 subject, 2.0%).
Conclusion: The reduced prevalence of current smokers among PD subjects as compared to healthy controls is consistent with previous findings, suggesting a possible neuroprotective effect of smoking. However, it could be due, at least in part, to the increased prevalence of former smokers among PD patients, that were more prone to quit smoking as compared to healthy controls. We suggest that smoking cessation could be an early preclinical condition occurring in PD.

1. Introduction

Parkinson's disease (PD) presents different possible determinants, and environmental factors such as lifestyle-related factors, seem to play a significant etiologic role [1]. Among different possible environmental factors, cigarette smoking has been widely studied. In particular, several epidemiological studies reported a 60–70% reduced risk of PD in smokers, when compared to non-smokers [1–4]. Apparently, this association is dose-dependent with reduced PD risk in relation to intensity and duration of smoking [4–6]. Furthermore, a positive effect of smoking on motor features has been reported with a delayed time to disability requiring dopaminergic therapy [7], and on non-motor symptoms (NMS), with an improvement of smell in PD [8].

Association between quitting smoking and PD is an intriguing matter, that has been poorly investigated so far. We may assume

* Corresponding author. Tel./fax: +39 089672328.
E-mail address: pbarone@unisa.it (P. Barone).

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that quitting smoking could be either a consequence of personality changes occurring in PD [9], or causative as one of the factors increasing the risk of developing PD over time. Large epidemiological surveys grouped former with current smokers, missing a separate analysis [2,10,11]. Some other studies suggested an overall reduced risk of PD for former smokers, lower than never smokers but higher than current ones [1,2,4], but the rate of former smokers is reported to be extremely variable among PD subjects, ranging from 15% up to 50% [5,12]. Interestingly, a recent study suggested that patients with PD are able to quit smoking more easily than controls and, thus, proposed that ease of smoking cessation is an aspect of premanifest PD [13].

The aims of our study are: 1) to assess the prevalence of current, former and never smokers between newly diagnosed and drug naïve PD subjects, and healthy controls; 2) to describe reasons for quitting smoking in PD, that have never been previously reported; 3) to evaluate the relationship between smoking status and motor and non-motor features of PD.

2. Materials and methods

2.1. Study design

Our study was designed to evaluate differences in smoking habits between de novo PD subjects and healthy controls. Secondary endpoints were describing reasons for quitting smoking, and evaluating possible relationships between smoking status and motor and non-motor symptoms of PD. The study was performed according to the good clinical practice guidelines and the Declaration of Helsinki.

2.2. PD subjects

We enrolled de novo, drug-naïve patients with parkinsonism who were consecutively referred to the Centre for PD and Movement Disorders at the Department of Neurosciences at the University "Federico II" of Naples, Italy, within 2008 and 2009. The local ethical committee approved the study and all subjects provided written informed consent. Inclusion criteria were: presence of a parkinsonian syndrome according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria [14,15]; onset less than 2 years before; no previous or current treatment with dopaminergic drugs. Additional criteria for inclusion were lack of significant cerebral lesions on MRI or CT. Exclusion criteria were: diagnosis of secondary (such as vascular and drug-induced) or familial parkinsonism, diagnosis of atypical parkinsonism, namely, multiple system atrophy, progressive supranuclear palsy, corticobasal syndrome, and dementia with Lewy bodies, according to current diagnostic criteria [16–20]. Parkinsonism was diagnosed by movement-disorder specialists experienced in parkinsonian disorders. All subjects were evaluated after 2 years in order to exclude subjects with symptoms and/or signs of atypical parkinsonism, as previously reported [16–20].

Demographics and clinical data were recorded. An expert physician evaluated motor features by means of Unified Parkinson's Disease Rating Scale (UPDRS) part III. In addition, all patients completed the NMS Questionnaire (NMSQ), a validated tool for detection of NMS [21]. The NMSQ consists of 30 questions with dichotomous (yes/no) answers and of a total score, which ranges between 0 and 30, with higher scores reflecting more NMS [21]. None of the patients was treated with anti-parkinsonian drugs, anticholinergic agents, choline esterase inhibitors, antidepressants, anxiolytic drugs, or other centrally acting substances that might have affected both motor and non-motor evaluation.

Smoking habits were recorded (smoking duration and intensity), and PD subjects were categorized according to self-reported smoking status as never, former, or current smoker [22]. In particular, current smokers were defined as those who had smoked 100 or more cigarettes in their lifetime and were smokers when the survey took place. Former smokers were those who reported as being smokers during their lifetime but currently did not smoke. In addition, ever smokers PD patients were asked about their age at starting and the number of cigarettes smoked per day. Moreover, former smokers were asked to report the age at quitting and the most important reason that led them to quit. For ever smokers (current and former smokers), we calculated pack-years, as previously suggested (packs of cigarettes per day multiplied by years smoked) [22]. Reasons to quit were categorized as previously suggested in similar surveys conducted in Italy [22–24]: illness and current health-related conditions (different from PD); physician's advice; knowledge of the harmful effects of smoking; pregnancy/birth of a child; economic reasons (cigarettes too expensive); pressure to quit by partner/relatives; other reasons.

2.3. Controls

Controls were recruited at the Occupational Medicine Unit of the same hospital within the same period. Concomitant diseases and treatments were recorded. All controls underwent physical examination according to clinical practice. Smoking habits were recorded, and controls were categorized according to participant self-report smoking status as never, former, or current smoker, as previously reported [22–24]. Since, unfortunately, reasons for quitting smoking were not assessed in our control group, an Italian survey on a large population presenting similar age range and geographical distribution was used for comparison with PD group [24].

2.4. Statistical analysis

First of all, PD subjects were matched to controls extracted from database of the Occupational Medicine Unit considering covariates (age and gender), by using the Propensity Score Matching (PSM), with a case/control matching ratio of 1/2. Demographic differences between groups were evaluated by χ^2, *t*-test or Mann–Whitney test, as appropriate. Comparisons between PD subjects and controls in relation to smoking status were conducted by a preliminary χ^2 test and by logistic regression analysis with odds ratio and 95% confidence intervals calculation. In order to study other possible factors interfering with smoking status, the latter model was corrected for age and gender. Subsequently, an additional categorization was performed and a logistic regression model analyzed difference in prevalence of ever smokers (former + current smokers) and never smokers between PD subjects and controls.

In order to examine secondary endpoints, a descriptive analysis was performed with different reasons to quit smoking in PD group. Differences in pack-years between current and former smokers have been analyzed by *t*-test and analysis of variance (ANOVA) corrected for age and gender. Furthermore, motor symptoms were evaluated by regression analysis studying the relationship between UPDRS part III and smoking status. In order to evaluate the quantitative relationship between smoking and motor symptoms in ever smokers (current and former), we performed a regression model considering pack-years and UPDRS part III. Among former smokers, time from cessation was related to UPDRS part III by regression analysis. With regard to non-motor symptoms, NMSQ total score was related to smoking status by regression analysis, and NSMQ single items were related to smoking status by χ^2 test or Fisher's exact test, as appropriate. Subsequently, Bonferroni correction for multiple comparisons was performed. In order to evaluate the quantitative relationship between smoking and NMS in ever smokers (current and former), we performed a regression model considering pack-years and NMSQ total score. Among former smokers, time from cessation was related to NMSQ total score by regression analysis.

Stata 12.0 and Microsoft Excel 2011 software were used for data processing and statistical analysis. Results were considered statistically significant for $p < 0.05$.

3. Results

We recruited 116 PD subjects that were matched to 232 healthy controls by PSM. No differences were found between cases and controls for age and gender (Table 1).

PD subjects and controls were found to be current smokers (7.7 vs. 39.6%), former smokers (43.9 vs. 6.5%) and never smokers (48.2 vs. 53.9%) (Table 2; Fig. 1). With regard to our primary endpoint, χ^2 test showed an association between PD diagnosis and smoking status ($p < 0.001$). In particular, at logistic regression analysis current smoking was less likely associated to PD diagnosis ($p < 0.001$), while smoking cessation was more likely associated to PD diagnosis ($p < 0.001$) (Table 2; Fig. 1). Age and gender did not appear to influence smoking status differences between PD subjects and controls ($p = 0.708$ and $p = 0.366$, respectively). Logistic regression failed to show any association between ever smoking (current and former) and PD diagnosis ($p = 0.324$), since there was no difference in prevalence of ever smokers and never smokers between PD subjects and controls.

Table 1
Demographics and clinical features of PD subjects and controls.

	PD subjects ($n = 116$)	Controls ($n = 232$)	*p*-value
Gender			
Male (%)	69 (59.5)	138 (59.5)	*0.945*
Female (%)	47 (40.5)	95 (40.5)	
Age ± SD (range)	59.4 ± 8.4 (40–74)	58.7 ± 7.5 (40–72)	*0.789*
UPRDR part III	15.2 ± 7.1		
NMSQuest total score	4.2 ± 3.2		

p-values from χ^2, *t*-test or Mann–Whitney test, as appropriate.
PD: Parkinson's disease; SD: standard deviation; UPDRS: unified Parkinson's disease rating scale; NMSQuest: non-motor symptom questionnaire.