Coffee Consumption and the Risk of Levodopa-induced Dyskinesia in Parkinson's Disease: The FRAGAMP Study

Giovanni Mostile, PhD,[1] Alessandra Nicoletti, MSc,[1] Giuseppe Nicoletti, MD,[2] Gennarina Arabia, MSc,[3] Giovanni Iliceto, MD,[4] Paolo Lamberti, MD,[4] Roberto Marconi, MD,[5] Letterio Morgante, MD,[6] Paolo Barone, MD,[7] Aldo Quattrone, MD, [2,3] and Mario Zappia, MD [1].

1 Dipartimento G.F. Ingrassia, Sezione di Neuroscienze, Università Degli Studi di Catania, Italy; 2 Istituto di Bioimmagini e Fisiologia Molecolare – Consiglio Nazionale delle Ricerche, Catanzaro, Italy; 3 Clinica Neurologica, Università "Magna Græcia" di Catanzaro, Italy; 4 Dipartimento di Scienze mediche di base, neuroscienze e organi di senso, Università di Bari, Italy; 5 Divisione di Neurologia, Ospedale Misericordia, Grosseto, Italy; 6 Dipartimento di Neuroscienze, Università di Messina, Italy; 7 Dipartimento di Medicina e Chirurgia, Università degli Studi di Salerno, Italy.

BACKGROUND

Parkinson's disease (PD) is the second most common neurodegenerative disease of the elderly. Current thinking is that mitochondrial dysfunction, oxidative stress, and protein mishandling have a central role in PD pathogenesis, and that in sporadic PD these processes are probably due to a complex interaction between genetic and environmental factors (de Lau et al, Lancet Neurol 2006). Several studies have been carried out to assess the relationship between coffee consumption and PD, showing a significantly decreased PD risk for coffee drinkers with fairly consistent results from both case-control as well as from large longitudinal studies (Hernán et al, Ann Neurol 2002).

Caffeine is the most widely consumed methylxanthine, and its most important pharmacologic effect at doses normally assumed through coffee drinking is an antagonistic action on the adenosine receptors. Interestingly, the adenosine A2A receptor modulates the nigrostriatal dopamine system, and antagonists of that receptor have been proposed as therapy for PD (Richardson et al, Trends Pharmacol Sci 1997). In particular different clinical trials have demonstrated that adenosine A2A antagonist, such as istradefylline, reduced daily OFF time in patients with motor complications on levodopa treatment (Mizuno et al, Mov Disord 2013; Zhu et al, Neurol Res 2014). On the bases of some evidence coming from experimental studies in animal models it has also been hypothesized that chronic administration of caffeine early in the course of PD may reduce the long-term risk of dyskinesia induced by levodopa therapy. In agreement with this latter hypothesis also a clinical study has recently supported the possibility that caffeine intake may reduce the likelihood of developing dyskinesia (Wills et al, Mov Disord 2013; Kanda et al, Int Rev Neurobiol 2014).

The FRAGAMP study ("Fattori di Rischio Ambientali e Genetici Associati alla Malattia di Parkinson", that is "Environmental and Genetic Factors in Parkinson's Disease") is a large multicenter case-control study carried out in Central-Southern Italy to evaluate the possible role of environmental and genetic factors in PD (Nicoletti et al, Neurol Sci 2010). In agreement with literature data also in the FRAGAMP study we found an inverse association between coffee consumption and PD risk with a significant trend dose-effect (Nicoletti et al, Mov Disord 2010).

AIMS

To determine the possible association between coffee consumption and risk of levodopa-induced dyskinesia in PD.

PATIENTS & METHODS

Study population

The FRAGAMP study: large multicenter case-control study involving five Movement Disorder centers located in Central-Southern Italy. Patients affected by PD diagnosed according to the Gelb's diagnostic criteria (Gelb et al, Arch Neurol 1999), were consecutively enrolled in the study.

All patients underwent a standard neurological examination using Hoehn–Yahr staging, Unified Parkinson's Disease Rating Scale (UPDRS).Mini Mental State Examination (MMSE) was administered to all the enrolled subjects in order to assess the presence of cognitive impairment and, to avoid the use of proxy responders and possible differences in the accuracy of recall, PD patients with a MMSE score lower than 24 were excluded from the analysis. Presence of levodopa-induced dyskinesia was assessed according to the item 32 of the UPDRS section IV, while severity of dyskinesia was evaluated using the Abnormal Involuntary Movement Scale (AIMS).

Ethics

The study was approved by the local ethical committee and patients and controls were enrolled only after signed the informed consent.

Exposure ascertainment

PD patients enrolled in the study underwent a face-to-face interview performed by trained neurologists using a standardized structured questionnaire. For coffee consumption, we collected information about the average number of cups per day and duration of intake. Data on cigarette smoking and alcohol consumption were also collected.

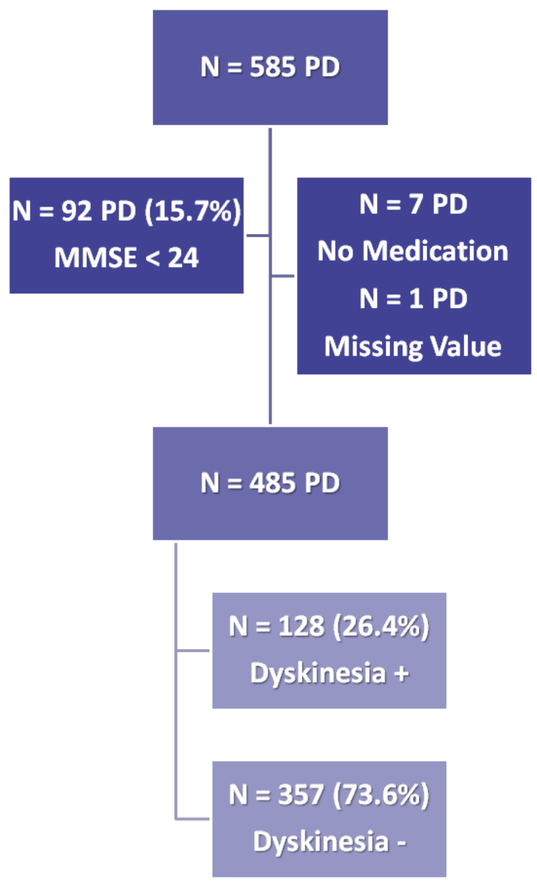
Statistical analysis

Unconditional logistic regression analysis was performed and for each study variable, we calculated OR, 95% Confidence Interval (CI), and p-value (two-tailed test, $\alpha = 0.05$). Multivariate analysis: parameters associated with the outcome at the univariate analysis with a threshold of $p = 0.10$ were included in the model. The model was manually constructed using the likelihood ratio test (LRT). To evaluate the role of dopaminergic therapy the Levodopa Equivalent Dose (LED) was calculated for those patients taking dopamine agonists. For quantitative exposure the test for linear trend was performed to evaluate the linear or trend effect.

RESULTS

Four hundred eighty-five PD patients (292 men; mean age 65.6 9.8) were enrolled in the study of whom 128 (26.4%) presented dyskinesia (Fig.1). Out of the 485 PD patients 439 (90.5%) were taking levodopa [200 (41.2%) levodopa alone and 239 (49.3%) levodopa in combination with dopamine agonists], while 46 (9.5%) were taking only dopamine agonists. Baseline characteristics, univariate and multivariate analysis are reported in Tab.1. Multivariate analysis showed a significant negative association between presence of dyskinesia and coffee drinking (ever *versus* never) with an adjusted OR of 0.44 (95%CI 0.23-0.85; *p-value* 0.01). We have also found a significant trend of decreasing risk with increasing number of cups per day (test for trend *p-value*<0.05) (Tab.1).

Fig.1. Study Population



Tab.1. Univariate and Multivariate analysis (unconditional logistic regression)

	Patients with Dyskinesia N = 128		Patients without Dyskinesia N = 357		Univariate analysis			Multivariate analysis†		
	N	%	N	%	OR	95%CI	p-value	AdjOR	95%CI	p-value
Gender										
Male	76	59.4	216	60.5	1	/	/			
Female	52	40.6	141	39.5	1.05	0.69-1.58	0.8			
Age*	64.5	9.2	66.0	10.0	0.98	0.96-1.00	0.1	0.94	0.91-0.98	0.001
Duration (years)										
0-6	24	18.9	246	70.3	1	/	/	1	/	/
>6	103	81.1	104	29.7	10.1	3.15-16.7	<0.0001	5.46	2.45-12.16	<0.0001
Age at onset*	53.2	11.6	60.8	9.9	0.93	0.92-0.95	<0.0001			
Hoehn–Yahr*	2.9	0.8	2.0	0.7	3.78	2.68-5.33	<0.0001	2.15	1.42-3.26	<0.0001
UPDRS-ME*	26.6	12.1	16.7	8.8	1.09	1.06-1.12	<0.0001			
Duration of treatment (months)*	101.8	63.9	43.2	47.4	1.02	1.01-1.03	<0.0001	1	1-1.01	0.04
Average LED	719.2	324.5	435.2	229.8	1.004	1.003-1.005	<0.0001			
0-500	40	31.5	239	68.3	1	/	/	1	/	/
>500	87	68.5	111	31.7	4.68	3.02-7.24	<0.0001	1.97	1.03-3.75	0.04
Coffee										
Never	53	41.4	81	22.7	1	/	/	1	/	/
Ever	75	58.6	275	77.2	0.42	0.27-0.64	<0.0001	0.44‡	0.23-0.85‡	0.01‡
Cups of coffee per day**										
None	54	42.2	82	23.0	1	/	/	1	/	/
1-3	66	51.6	243	68.1	0.41	0.27-0.64	<0.0001	0.49	0.25-0.94	0.03
>3	8	6.2	32	8.7	0.38	0.16-0.88	0.02	0.16	0.03-0.77	0.02
Cigarette smoking										
Never	86	67.2	228	64.2	1	/	/			
Ever	42	32.8	127	35.8	0.88	0.57-1.34	0.5			
Wine drinking										
Never	89	69.5	224	62.9	1	/	/			
Ever	39	30.5	132	37.1	0.74	0.48-1.15	0.2			

Legend: Whenever variables were dichotomized or polychotomized, the cutoffs were derived from the pooled distribution of cases and control subjects (e.g., using the median, tertiles, or quartiles); LED = *Levodopa Equivalent Dose;* *continuous variableare expressed as mean SD; **test for trend p-value <0.05*;* †In multivariate analysis coffee consumption was included as a categorical variable with different levels of exposure. The model was manually constructed using the likelihood ratio test (LRT) and ORs were adjusted by age, disease duration, Hoehn-Yahr stage, average LED intake, duration of treatment; ‡Estimates were computed using a different multivariate model which included coffee consumption as binary variable (ever/never) and the same covariates specified above.

CONCLUSIONS

Our findings provide evidence that chronic administration of caffeine may reduce the long-term risk of levodopa-induced dyskinesia in PD patients.

The size of our sample, the direct face-to-face interview and the complete neurological examination represent the main strengths of our study. However we are aware that, due to the retrospective design, possible recall bias cannot be excluded.