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GENETICS, DRUGS AND ENVIRONMENTAL FACTORS IN PARKINSON'S DISEASE

A CASE-CONTROL STUDY

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ABSTRACT - A case-control study of Parkinson's disease (PD) was conducted in the city of Rio de Janeiro based on the assumption that neurotoxins with secondary parkinsonian action may be related to the development of Parkinson's disease. Ninety-two subjects with PD and 110 controls were queried through a questionnaire in order to investigate possible risk factors for the disease. The following factors were studied: herbicides/pesticides, exposure to chemicals, ingestion of drugs with secondary PD effects, rural life, water well source, family history, cranial trauma and cigarette smoking. Study of mentioned factors was achieved through univariate, stratified and multivariate analyses. Univariate and multivariate analyses demonstrated that PD was positively associated with family history (OR = 14.5; CI = 2.98 - 91.38), with the use of drugs with secondary PD action (OR = 11.01; CI = 3.41 - 39.41) and with exposure to chemical agents (OR = 5.87; CI = 1.48 - 27.23). PD was found to be inversely associated with cigarette smoking (OR = 0.39; IC = 0.16 - 0.95). Stratified analysis only confirmed family history and drug use, besides demonstrating that cigarette consumption could be a protection factor, when aforementioned factors were involved. This study might be a warning as to the cares that need to be taken regarding drug use and occupational exposure to chemical agents, as both types of substances present secondary PD action.

KEY WORDS: Parkinson's disease, genetics, chemical agents, drugs, environmental factors.

Genética, medicamentos e fatores do meio ambiente na doença de Parkinson

RESUMO - Um estudo caso-controle foi realizado na cidade do Rio de Janeiro, partindo-se do pressuposto de que neurotoxinas com ação parkinsoniana secundária poderiam facilitar a ocorrência da doença de Parkinson. Noventa e dois pacientes com doença de Parkinson e 110 controles foram avaliados através de questionário para a investigação de possíveis fatores de risco para a doença. Foram pesquisados os seguintes fatores: herbicidas e pesticidas, exposição a agentes químicos, uso de medicamentos com ação parkinsoniana secundária, vida rural, ingestão de água de poço, história familiar, passado de trauma central e consumo de cigarro. O estudo destes fatores foi realizado através das análises univariada, estratificada e multivariada. As análises univariada e multivariada demonstraram que a história familiar (RC = 14,5; IC = 2,98 - 91,38), o uso de medicamentos (RC = 11,01; IC = 3,41 - 39,41) e a exposição a agentes químicos (RC = 5,87; IC = 1,48 - 27,23) eram positivos como fatores de risco para a doença. Papel inverso foi ocupado pelo consumo de cigarros (RC = 0,39; IC = 0,16 - 0,95). A análise estratificada confirmou apenas história familiar e medicamentos como fatores de risco, além de demonstrar que o consumo de cigarros poderia ser um fator de proteção, quando houve alguma participação destes mesmos fatores. Este estudo talvez possa alertar quanto aos cuidados que devem ser tomados na utilização de drogas e na atividade ocupacional com agentes químicos, quando estes dois tipos de substâncias apresentam efeitos parkinsonianos secundários.

PALAVRAS-CHAVE: doença de Parkinson, genética, agentes químicos, drogas, fatores ambientais.

Recent studies on etiology of Parkinson's disease (PD) chiefly point to a genetic predisposition associated to a possible participation of internal and or external neurotoxins. Over the last decade,

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numerous studies showed the participation of external toxins in the genesis of the disease. Evidence of an inadequate performance of the cytochrome P-450 enzymatic complex in PD reinforced the idea of the occurrence of deficient metabolizing of xenobiotic substances, which led to the hypothesis that parkinsonian patients are more vulnerable to the action of some neurotoxins[1]. One of the studies investigated the participation of cytochrome P-450 2D6 (CYP2S6) and M1 S-transferase glutathione (GSTM1) genes, whose action is based on the programming of enzymes responsible for detoxification of external toxins. It could be observed that individuals who posses the CYP2D6L allele have 2.4 times more chances of being affected with PD than controls. Furthermore, if the individual has the M1 S-transferase (GSTM1) the possibility is increased from 11 to 14 times[2]. On the other hand, some diseases can be transitory — disseminated lupus erythematosus, myasthenia gravis, scleroderma, diabetes and arterial hypertension — triggered by the simple action of a drug, and it is not uncommon that such diseases only come to their full clinical development many years later. So, one might suspect that some cases of transitory parkinsonism represent a symptomatic expression of PD, which was only transitorily facilitated by the action of a specific neurotoxin. The presence of correlated risk factors in transitory parkinsonism and in PD also support this concept. This becomes clear, for example, when family history and use of chemical agents are observed in both syndromes[3,4].

In 1986, Calne et al.[5] proposed that diseases like Alzheimer's, Parkinson's and amyotrophic lateral sclerosis were determined by an environmental agent which was responsible for long-term progressive damage, with clinical manifestations only occurring after age-related neuronal losses. Regarding PD, Langston[6] proposed that substantia nigra neurons react in the presence of a toxin, with a subsequent reduction in their number. In view of dopamine loss resulting from this action, there is an activation of the oxidative compensatory metabolism, which would be responsible for the increase of dead neurons in the substantia nigra. The finding that clinical, biochemical, and pathological features of PD are caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP)[7] suggests that a similar neurotoxin may trigger PD. Evidence obtained through reduction positron emission tomography of the progressive damage of dopaminergic function of patients exposed to the MPTP adds up to this hypothesis[8]. This fact by itself suggests the existence of damage "in-progress" of the substantia nigra neurons. Initial evidence that could lead to explain MPTP's possible action in the cell, was described by Nicklas et al.[9], demonstrating that the MPP+ is a potential inhibitor to the NADQ Co Q1 reductase, or Complex I, of the mitochondrial respiratory enzymatic chain. Some years later, other studies demonstrate that there was an important reduction in the activity of the NADQ Co Q1 reductase of the substantia nigra mitochondrian neurons in parkinsonians, suggesting that this deficiency could be related to the onset of the pathological process of PD[10]. This same kind of deficiency of the respiratory enzymatic chain was also considered as secondary due to the action of neuroleptics and calcium antagonists[11,12]. Some studies are also disclosing the fact that drugs with parkinsonian action can cause neuronal injury in the substantia nigra[13], and this can increase PD risk. Besides that, it has been observed that an increase of circa 18% in PD incidence occur in elderly patients who made use of neuroleptics, monitored for a minimum period of 21 months even prior to PD diagnosis[14].

In view of such data, and coupled with the easy over-the-counter sale of drugs with parkinsonian secondary action in Brazil, we decided to conduct a case-control-study in the city of Rio de Janeiro. The goal was to determine the relative etiologic significance on the development of PD of factors such as: rural living, potable water well-source, central or peripheral trauma, family history, herbicides and insecticides, cigarette smoking, occupational exposure to chemical agents, and use of drugs with secondary parkinsonian action.

METHOD

The city of Rio de Janeiro has a population of approximately 5 000 000 inhabitants and is the capital city of the State of Rio de Janeiro. Between January 30, 1996 and February 1, 1997, subjects diagnosed with PD (n = 92) were randomly selected at the Neurology Department of IASERJ Central Hospital (Instituto de Assistência

aos Servidores do Estado do Rio de Janeiro), located in the center of the city. Controls (n = 110) were selected in the same hospital and were matched to subjects according to sex and age (± 2 years). All controls underwent examination and those showing any parkinsonian or dementia signs were excluded. Distribution of diagnoses among control patients was: rheumatoid arthritis (1.2%), sciatica (11.9%), migraine headache (12.5%), tension headache (8.1%), dizziness (36%), polyneuropathy (26.1%) and myelopathy (4.2%).

All subjects were examined at least more than once by the same neurologist (ALW). Subjects with atypical features suggesting other forms of secondary parkinsonism, severe dementia or any history of cerebrovascular disease were excluded. Participants received a questionnaire (Chart 1) to be filled out during a face-to-face interview with the examiner. Questionnaire test-reliability was initially assessed with a small group of subjects (n = 5). Phase two took place 1 month later. No relevant variance between time points could be evidenced in all variables. The interviewer was not blind to respondent case versus control status, although the purpose of the study was not revealed to respondents. For PD diagnosis, criteria proposed by Calne et al.[15] were used for a definitive diagnostic associated to stage 3 of the UKPDB[16]. For the ruling out of this diagnosis, step 2 of the UKPDB was used[17].

Risk factors were investigated as follows: 1 – Rural living prior to appearance of signs and symptoms: the individual had to have lived in this kind of environment for a period never inferior to 15 years; 2 – Potable water-well source: for a minimum period of 15 years before appearance of symptoms. 3 - Inhaling and/or handling herbicides and/or pesticides: a minimum period of 15 years in contact with such substances was deemed necessary for entry. 4 - Cigarette smoking: as a protective factor, a minimum period of 8 years of consumption was required. If the individual reported that consumption had been suspended during the last 2 years prior to the onset of disease, this variable was taken into consideration. 5 - History of central or peripheral nervous system trauma: when central trauma was reported, besides its temporal relation to the individual, it had to have happened concurrently with important symptoms, like transitory consciousness loss or even headache and/or dizziness lasting for more than 2 days after the occurrence of trauma. 6 - Drugs with parkinsonian effects: to bear any relation to PD, the use of such drugs had to have lasted for a minimum period of one year, besides the fact that its use should have been suspended at least one year prior to the onset of the evolution symptoms of the disease. 7 - PD family history: subjects should report any relatives with the disease, with additional information on the evolution of symptoms for each individual. 8 - Inhaling or handling chemical agents with parkinsonian action: a minimum period of 15 years in contact with such substances was required.

The method consisted of an investigation through univariate, stratified and multivariate analyses. 1 - Univariate analysis: data obtained from evaluation of variables were examined as follows: a) X2 no parametric test (chi-square) indicated for the identification of tables that use crossed frequencies, aiming to examine the occurrence of associations among the factors. If any of the cells presented a frequency of less than 5, Fisher's

Chart 1. Questionnaire distributed to all investigated patients.

1. Identification; Origin; Occupation; Date of birth; Place of birth; Place of residence; former places of residence.

2. Used to drink well-water in any of the places where you lived? For how long?

3. Have you regularly inhaled or handled herbicides and insecticides? For how long?

4. Do you deal or have you ever dealt with grains or seeds? For how long? Were these chemically-treated foods?

5. Ever inhaled or handled chemical substances? Which ones? For how long?

6. Your place of residence is or was located near any chemical industries or plants? What kind of industry? For how long?

7. Ever suffered any important head trauma?

8. Have you got any relatives diagnosed with Parkinson's disease? How did you get to know about their diagnosis?

9. Do you smoke or have you ever smoked? How much and for how long?

10. Can you name any drugs that you have used daily for more than one year? For how long and when?

11. Which drugs have you used during the last year?

exact test would then be used. b) Odds ratio related to frequency values, and also as a means to interpret the influence of some specific factors related to PD occurrence. Methodology applied took into account the significance level probability of 5% ($p < 0.05$). 2 - Stratified analysis: conducted to confirm variables that could provide significant statistical representation by confronting data obtained from these variables and also to assess to what extent one variable can influence the others. 3 - Multivariate analysis: its purpose was to avoid any bias resulting from combined effects among factors. This was effected based on a model of logistic regression, and individual analysis of parameters was used to complement data.

RESULTS

Forty-one men and 51 women diagnosed with PD were compared to controls (47 men and 63 women). Average age was 70.55 for PD patients and 68.38 for controls. Present age of subjects with PD (n = 92) ranged from 55 to 78, while controls (n = 110) ranged from 55 to 79. In the group of subjects, 5 individuals were brown and 5 black-skinned; among controls, 12 were brown and 7 were black.

A) Family history: Among subjects, 20.65% (17/92) had a family history of PD. Regarding distribution of relatives affected by the disease, it was found that first degree relatives were associated to 12 cases, second degree relatives were observed in 5 cases, and third degree relatives appeared in 4 cases. Only two controls had a family history of PD.

B) Herbicides and pesticides: From the total of selected individuals for this factor, 6 were diagnosed with PD (6.36%) compared with 3 controls (2.72%). Among the cases where contact with these compounds was reported, 4 individuals had used them during rural residency (all had PD), while the remaining ones had used them in their own houses.

C) Chemical agents: 14 subjects and 4 controls were included. Table 1 shows the chemical products involved. Occupations were: painters, dentists, goldsmiths and car mechanics.

D) Drugs: this variable was present in 22 cases of PD (23.9%); 5.43% of subjects reported not having any perception of parkinsonian symptoms while using mentioned drugs. Four controls (3.63%) with a history associated to the use of parkinsonian drugs were noted. Table 2 shows distribution of drugs involved among subjects and controls.

E) Trauma: 17 subjects (18.5%) had some relevant history of head trauma, compared with 14 controls (12.7%).

F) Rural living: 26 subjects (28.3%) and 31 controls (28.2%) matched necessary criteria for this variable.

G) Potable water well-source: 26 subjects (28.3%) and 23 controls (20.9%) had a history of well-water intake.

H) Cigarette smoking: 9 subjects (9.8%) and 24 controls (21.8%) were cigarette smokers.

Table 1. Chemical agents among 92 patients with Parkinson's disease

Chemical agent	Controls	PD
Methanol	0	1
Toluene	2	2
Cyanide	0	2
Mercury	1	4
Petroleum products	1	5
Total	14	14

PD, Parkinson's disease.

Table 2. Presence of drugs with parkinsonian action in 92 cases of Parkinson's disease (use during a period of 1 year prior to the symptoms beginning).

Drug	Controls	PD
Cinnarizine	2	7
Diltiazem	0	4
Amiodarone hydrochoride	0	3
Sulpiride	1	3
Lithium	0	2
Pericyazine	0	1
Verapamil	1	1
Alphamethyldopa	0	1
Total	4	22

PD, Parkinson's disease.

Table 3. Association between Parkinson's disease and variables.

Variable	Odds Ratio	Confidence Interval (95%)
Rural Life	1	(0.52, 1.95)
Well-water	1.49	(0.74, 3.01)
Herbicides / insecticides	2.49	(0.53, 13.14)
Trauma	1.55	(0.67, 3.62)
Drugs	11.01	(3.41, 39.41*)
Family history	14.05	(2.98, 91.38*)
Cigarette consumption	0.39	(0.16, 0.95)
Chemical agents	5.87	(1.48, 27.23*)

Table 4. Association of Parkinson's disease with the use of drugs and family history, controlled by cigarette consumption.

	Cigarette consumption			
	Yes		No	
	Odds Ratio	Confidence Interval (95%)	Odds Ratio	Confidence Interval (95%)
Use of drugs	6.57	(0.36, 221.95*)	11.93	(3.18, 52.79*)
Family history	11.5	(0.78, 356.91*)	20.3	(2.68, 427.95*)

Table 5. Association between Parkinson's disease and cigarette consumption, controlled by use of drugs.

	Use of drugs			
	Yes		No	
	Odds Ratio	Confidence Interval (95%)	Odds Ratio	Confidence Interval (95%)
Cigarette consumption	0.24	(0.01, 9.17*)	0.44	(0.16, 1.17)

1) Univariate analysis: Table 3 displays results. This method demonstrated that the considered risk factors for the disease were distributed by odd terms as follows: family history 14.05 (CI = 2.98 - 91.38), drugs 11.01 (CI = 3.41 - 39.41), chemical agents 5.87 (CI = 1.48 - 27.23), and cigarette smoking 0.39 (CI = 0.16 - 0.95). The obtained confidence intervals for drugs, chemical agents and family history were considered as inaccurate.

2) Stratified analysis: Drugs and family history variables were confirmed as risk factors, while cigarette smoking was considered a protection factor. Results obtained were: 1 – PD association to the use of drugs presented variations in relation to the odds ratio for the drugs variable (Table 4). Its value of 11.01 (CI = 3.41 - 39.41) underwent the following variations: a) If analyzed among smokers it falls to 6.57 (CI = 0.36 - 221.95); b) Among non-smokers it becomes stable at 11.93 (CI = 3.18 - 52.79). 2 – PD associated to family history indicated that the odds ratio value that was 11.5

(CI = 0.98 - 356.91) among smokers rose to 20.3 (CI = 2.68 - 427.95) among non-smokers. 3 – Cigarette consumption odds ratio underwent the following alterations in relation to use of drugs (Table 5): a) If analyzed among those that made use of drugs, its value is 0.24 (CI = 0.01 - 9.17); b) Among those who did not make any use of drugs, the value is 0.44 (CI = 0.16 - 1.17).

3) Multivariate analysis: This process used the logistic regression method, where values pertaining to the parameters' estimates (PE), X2 test (chi-square), are presented together with the significance level. Methodology applied considered significance level (SL) equivalent to a probability of 5% ($p < 0.05$). In order of decreasing importance, factors bearing significant values for PD were: drugs (SL = 0.0001; X2 = 27.58; PE = 2.973), family history (SL = 0.0006; X2 = 4.4; PE = 2.733) and chemical agents (SL = 0.0014; X2 = 10.19; PE = 2.214). No significant values were found associated to rural residency (SL = 0.138; X2 = 2.2; PE = - 1.26), well water (SL = 0.211; X2 = 1.56; PE = 1.12), herbicides and pesticides (SL = 0.271; X2 = 1.21; PE = 0.887) and trauma (SL = 0.887; X2 = 0.02; PE = 0.067).

DISCUSSION

Rural living, potable well-water source, trauma, and herbicides/pesticides variables were considered as of irrelevant statistical value. Due to contradictory studies about a possible protective action of cigarette smoking against PD, a broad survey about the possible protective action of cigarettes in case of PD[18] is deemed necessary. After analyzing 46 studies related to this issue, using the statistical method, one may come to the conclusion that cigarette smoking is capable of protecting against PD. According to the authors, it would be possible that some tobacco component could act as a protection for neurons against ambient toxins.

Univariate analysis showed only a slight cigarette protective action against PD. In stratified analysis, the use of drugs among non-smokers was found to be responsible for a decrease of approximately 40% of the odds ratio. On the other hand, it did not present variation when confronted with smokers. Otherwise, if the cigarette consumption odds ratio is analyzed only among those that made use of drugs, there is a small reduction from 0.39 to 0.24. Still, there is a moderate increase in the cigarette smoking odds ratio if considered among those who did not make use of parkinsonian drugs. It could be also verified that family history odds ratio shows a decrease of 20% when considered among non-smokers, the opposite occurring among smokers, and in this case, there is an increase of approximately 42%. Although, as noted in a restricted number of cases, these results seem to increase the possibility of cigarettes having a protective action against the development of the disease. But, if it is really so, it is more related to those cases where external toxins and family history have some participation. As possible corroboration to this finding, there is a study on cigarette protective activity in drug-induced parkinsonism[19].

Bibliographical revision about the role of heredity in PD conferred upon it an autosomal character of the dominant kind with reduced penetration[20]. Reports of familial cases indicated a higher genetic participation in PD[21]. The possibility of simultaneous exposure to the action of environmental toxins within the same family was observed among hypotheses for genetic participation in PD[21]. It does seem possible that, in some cases, some kind of genetic mutation might have occurred which led to the onset of PD in the individuals affected.

In the present study, from the viewpoint of causality, univariate and multivariate analysis pointed to family history as a PD risk factor. In the group of subjects, 19 cases (20.65%) were noted. Results reflect previously reported studies and this fact could possibly be explained if one observes that some subjects had a previous history of drug-induced parkinsonism, as it can be noted in some reports[3,4]. Thence, when genetic analysis of parkinsonian syndrome was effected, it became a complex task to distinguish cases of drug-induced parkinsonism from PD itself. Martin et al.[22] postulated that the mechanism of drug-induced parkinsonism can be related to PD. In other words, some patients presenting such transitory syndrome are perhaps also indicating some kind of genetic predisposition

to PD. According to the authors, some individuals affected by transitory parkinsonism might present an inadequate activity of the tyrosine hydroxilase enzyme. This hypothesis was based on a study by Chase et al.[23] that observed low levels of homovanillic acid in parkinsonian patients, after these patients had been treated with phenothiazine. On the other hand, the levels of mentioned acid were found to be high among individuals not presenting the syndrome.

Another aspect to be considered in relation to a predisposition for PD in some patients with drug-induced parkinsonism refers to the cytochrome P-450 hepatic enzymatic family, whose deficiency of the hydroxylation mechanism of the debrisoquine substance has been described in at least 75% of the patients with PD[24]. Also, it is known that this failure is related to the autosomal recessive heredity that is mediated by the mutant allele "n". So, it would not be surprising to expect that some drugs with xenobiotic behavior could be responsible for an abnormal accumulation of these substances in the blood of patients presenting difficulties to metabolize them.

The negative aspect found in relation to herbicides and pesticides could be possibly related to the field study area, with an irrelevant agricultural productivity. A study showed that mentioned substances can trigger parkinsonism[25]. Many epidemiological investigations have been directed towards the search for an environmental substance whose structure and action mechanism would be similar to MPTP. One of the aspects that could influence the toxicity of such agents seems to be related to an individual predisposition for the development of PD. The hypothesis that points to the premature onset of the disease in some patients might perhaps explain the higher sensibility of such individuals to the action of mentioned substances[24], just because of the higher number of inherited failures of the recessive kind for the hepatic hydroxylation function.

Most reports mentioning the association between chemical agents and parkinsonism denote isolated cases, in general with complete remission of the parkinsonian syndrome[4]. One of the exceptions is the appearance of symptoms similar to PD when related to MPTP[7,26]. Some very controversial data can be found in epidemiological literature about the role of chemical agents in PD. Semchuck et al.[27] could not obtain positive results for analyzed factors in relation to the following items: mineral oil, aluminum, carbon monoxide, cyanide, manganese and mercury. Tanner et al.[28], in a study carried out in China, attributed the low number of cases in that country to the lack of technological development in agriculture. A case-control study conducted with the multiethnic population of Singapore found high levels of mercury in both urine and hair of patients with PD[29]. Recently, Gorell et al.[30] found positive results in a group of patients who were in contact with metals for more than 20 years of occupational activity. Participation of such metals was made evident by the obtained values odds ratio for copper (OR = 10.61%; CI = 1.06, 105.83). It also became evident that combinations of metals such as steel/copper, steel/iron and copper/iron increased PD risk. Authors believe that the presence of such metals could have favored an increase in the generation of free radicals in the substantia nigra.

The first account of transitory parkinsonian syndrome following petroleum intoxication was published in 1994[31]. Among petroleum components, pyridine, toluene and benzene can be found, and all these compounds cause parkinsonian effects. Previous descriptions mentioned petroleum components as being responsible for isolated cases[4]. In five cases there was a history of chronic exposure to petroleum products. Univariate and multivariate analysis confirmed an association with chemical agents, demonstrating a discreet presence of this variable for PD risk. Positive family history was found in 5 of the 14 cases obtained in relation to such substances.

In 1982, Rajput et al.[32] described anatomopathological findings of two cases with previous history of neuroleptic-induced transitory parkinsonism. Necropsy findings showed PD characteristics, which led the authors to postulate that such individuals already had the disease in a pre-clinical state when parkinsonian manifestations started to occur. The publication referring to the three cases with initial parkinsonian diagnosis was replaced by PD itself, also led to the hypothesis that these patients presented sub-clinical PD when symptoms occurred. Some authors warned about a possible

participation of drugs with parkinsonian effect in the genesis of PD[14,33]. Notwithstanding, none of the epidemiological studies considered the use of drugs as a risk factor for PD. On the contrary, what can be noted in many papers, is the fact that patients that make or made use of medication with parkinsonian action are not taken into consideration. The exclusion of this factor in epidemiological studies of PD is perhaps related to the strict control regarding over-the-counter sale of medication in the countries where such investigations were carried out. Conversely, it was not by chance alone that the first cases of calcium-antagonist-induced parkinsonism were reported in Brazil and in Uruguay[34,35], countries where a strict control regarding the use of medicines is inexistent.

Some studies about the metabolism of neuroleptics demonstrated that such drugs, besides having a similar structure to MPTP, also form MPP+ similar compounds in their catabolism[36]. Moreover, they are also capable of causing damage to the respiratory enzymatic chain[11] and to the substantia nigra itself[13]. The respiratory enzymatic chain can be affected in the same way, both in PD and in the toxic injuries provoked by MPTP, neuroleptics, and calcium antagonists. It seems acceptable that drugs capable of altering the dopamine metabolism, an indispensable neurotransmitter to cellular physiology, may also have some kind of repercussion upon the survival of dopaminergic neurons. Evidence of a 20% reduction in the activities of Complexes I and II/III in the mitochondria of untreated patients with PD contribute to this hypothesis[37]. This indicates that this kind of alteration can be aggravated if in the presence of substances with the same effect, as reported in other studies[11,12]. In the same way, calcium antagonists may also be aggressive to the respiratory enzymatic chain[12]. Furthermore, this group of drugs has a blocking competitive action of D2 receptors in the striatum[38] that would facilitate the expression of parkinsonian symptoms.

Some studies report a low assimilation of F-dopa in the putamen of patients with persistent parkinsonism, when triggered by neuroleptics. In elderly patients affected by this syndrome, the appearance of an hyperintensity image in the nucleus caudatus was reported[39]. Another study, using MRI, made evident that the images of hypointensity in the putamen were predominant in youngsters, while those of hyperintensity in the striatum could be observed in elderly patients[40]. According to the authors, the presence of hypointensity images in the putamen of young patients could be related to a direct and toxic effect of this kind of drug, while the images of hyperintensity in the striatum observed in elderly people, were maybe related to vascular factors, depending on the age of such patients. The eventual participation of drugs favoring higher levels of iron deposit in basal ganglia can be also observed[41], a fact that would favor this metal turnover. Through positron emission tomography, it has been recently demonstrated that isolated loss of dopaminergic terminals in the posterior putamen suffices to the expression of the motor manifestations of the disease[42].

The present study seems to support the hypothesis that genetic and exposure to drugs or chemical agents with secondary parkinsonian action is associated with an increased risk for PD.

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