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Clinical and environmental risks factors associated with Parkinson's disease in Yucatan

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Abstract

Objective: *The objective of the study is to identify the risk and protective factors associated with Parkinson's disease (PD) in inhabitants of Yucatan.* **Methods:** *Case control study. A questionnaire with the main risk and protective factors for PD described in the literature was applied to cases and controls.* **Results:** *The sample consisted of 85 cases and 124 controls. In the univariate logistic regression analyzes, it was found that the following factors were significantly associated with a higher risk of developing PD: family history of PD (OR = 5.28, p = 0.001), personal history of diabetes (OR = 2.35, p = 0.01), the number of head trauma (OR = 1.35, p = 0.02), number of general anesthesia received (OR = 1.27, p = 0.050), exposure to organic solvents (OR = 2.73, p = 0.02) and the years of exposure to organic solvents (OR = 1.05, p = 0.01):* **Conclusions:** *The findings of this research indicate that the inhabitants of the state of Yucatan are exposed to the following risk factors: having a relative with PD, personal history of diabetes, number of head traumas, exposure to organic solvents, years of exposure to organic solvents and number of general anesthesia received.*

Keywords: *Case-control study. Parkinson's disease. Risk and protection factors. Head trauma. General anesthesia.*

Factores de riesgo clínicos y ambientales asociados a la enfermedad de Parkinson en Yucatán

Resumen

Objetivo: *Identificar los factores de riesgo y de protección asociados con padecer la enfermedad de Parkinson (EP) en habitantes de Yucatán.* **Métodos:** *Estudio de casos y controles. Se aplicó un cuestionario con los principales factores de riesgo y protección de EP descritos en la literatura tanto a los casos como a los controles.* **Resultados***: La muestra estuvo constituida por 85 casos y 124 controles. En los análisis de regresión logística univariados se encontró que los siguientes factores se asociaron significativamente a un mayor riesgo de desarrollar la EP: antecedente familiar de EP (RM = 5.28, p = 0.001), antecedentes de diabetes (RM = 2.35, p = 0.01), el número traumatismos craneoencefálicos (RM = 1.35, p = 0.02), número de anestesias generales recibidas (RM = 1.27, p = 0.050), la exposición a solventes orgánicos (RM = 2.73, p = 0.02) y los años de exposición a solventes orgánicos (RM = 1.05, p = 0.01):* **Conclusiones:** *Los hallazgos de esta investigación indican que los habitantes del estado de Yucatán están expuestos a los siguientes factores de riesgo: tener un familiar con EP, antecedentes personales de diabetes, el número de traumatismos*

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craneoencefálicos, la exposición a solventes orgánicos, los años de exposición a solventes orgánicos y número de anestesias generales recibidas.

Palabras clave: *Estudio de casos y controles. Enfermedad de Parkinson. Factores de riesgo y protección. Traumatismos craneoencefálicos. Anestesia general.*

Introduction

It is estimated that there are approximately 6.2 million people with Parkinson's disease (PD) in the world, by the time 2040 there will be 14.2 million people with PD and due to its rapid increase, some authors have considered declaring it a non-infectious pandemic[1]. Two hundred years have passed after the first description of PD by James Parkinson and various hypotheses have been put forward about its cause, but none have been conclusively proven[2-4].

PD is currently believed to have a multifactorial origin, being the result of a complex interaction between genetic and environmental factors, some of which confer risk, while others provide protection[2,3,5]. Among the clinical risk factors associated with the development of PD, the following have been frequently described: family history of PD and essential tremor, a personal history of diabetes, head trauma, general anesthesia, and other factors[5-8]. Among the environmental risk factors associated with PD, the following have been described: exposure to organic solvents, pesticides, herbicides, consumption of well water, and others[5,9,10]. As protective factors, caffeine consumption, smoking, and sports have been found, among others[11,12].

The Mexican population is aging, which allows us to suppose that, in the future, PD could be a public health problem, so it is necessary to have epidemiological data on this disease to anticipate trends and plan care needs[13]. Likewise, each region has its own social, cultural, and environmental characteristics. Yucatan is a region with a high impact of water contamination due to it has a karst type soil favoring contaminants entry into the phreatic level. There is evidence of contamination of the Yucatan aquifer, the only source of fresh water in the area, by organochlorine pesticides, as well as its bioaccumulation in the blood of women with cancer and breast milk, due to agricultural activities[14,15].

This would be the second on risk and protective factors associated with PD in Mexico, which could provide knowledge about the study dynamics of PD in different regions of Mexico, allowing the identification of people who would be at risk of Parkinson[16].

Objective

The objective of the study is to identify the risk and protective factors associated with Parkinson's disease in inhabitants of the state of Yucatan.

Material and methods

This is an epidemiological, observational, analytical, retrospective, case-control study. The protocol was reviewed and approved by the Ethics Committee of the Research Center "Dr. Hideyo Noguchi" in Mérida. Participants who met the inclusion criteria and who agreed to participate by signing an informed consent were included in the study. The study was conducted from May 2016 to May 2019.

This was a non-probability convenience sample. The sample consisted of patients diagnosed with Parkinson's disease by a neurologist. In the original design, it was intended to gather a sample of 100 patients and 100 controls, if the number of cases were less than 100, two controls would be used for each case. However, in the study period, only 85 cases and 124 controls were interviewed. A questionnaire designed to collect data on clinical and environmental variables considered as possible risk or protective factors for Parkinson's disease was applied to the cases and controls. The inclusion criteria were: patients diagnosed with PD by a neurologist; patients who have resided in Yucatan for at least 10 years prior to the date of their PD diagnosis; patients who signed an informed consent letter to participate in the study.

The elimination criteria were: patients who did not respond completely and correctly to the questionnaire designed for the study; patients who decided to withdraw voluntarily before completing the questionnaire; patients whose diagnosis was reversed or modified by a neurologist.

The control group was made up of participants matched with the group of cases by sex and age (± 3 years). Their inclusion criteria were: people who do not have PD, people who have resided in Yucatan for at least 10 years before the date of the PD diagnosis of their respective control; people who signed an informed consent letter to participate in the study. The elimination criteria were: people who did not respond completely and correctly to the questionnaire designed

for the study; people who decided to withdraw voluntarily before completing the questionnaire.

The clinical and environmental variables that were analyzed as possible risk factors associated with PD were: family history of PD, family history of essential tremor, head trauma, number of head trauma, number of times of unconsciousness due to head trauma, having been exposed to general anesthesia and the number of times this occurred, using pesticides, herbicides, and organic solvents, as well as the number of years of exposure to these, and well water consumption. The variables that were analyzed as possible protective factors were: smoking, consumption of caffeinated beverages, and physical activity.

Statistics analysis

The statistical analysis of the risk factors was carried out using the statistical package Statistical Package for the Social Sciences (SPSS). Univariate and multivariate logistic regression analyzes were performed on the variables under study to determine their contribution as possible risk and protection factors for PD. To calculate the strength of the association between each of factors and PD, the odds ratio (OR) was used, with a 95% confidence interval. In all cases, a test was considered significant when it was $p < 0.05$.

In the first phase, to estimate the relative risk of each of the variables, a univariate logistic regression analysis was performed individually with each one of them. Finally, with those factors that were significant in the univariate analysis, multiple logistic regression models were made in order to create models with those variables that remained significant and to be able to adjust for those confounding factors that could affect the risk estimation.

Results

The sample consisted of 85 cases and 124 controls. The mean age (± standard deviation) of the cases was 65.6 ± 10.1 years and the age of the controls was 64.3 ± 10.5 years. Fifty-one patients had two controls, 22 patients only one control, matched by age and sex, the remaining 12 patients had no control by age and sex. In the cases, 58 (68.2%) were men and 27 (31.7%) were women, which corresponds to a ratio of 2.1 men for every woman.

Univariate logistic regression

Table 1 shows the results of the univariate logistic regression analysis of clinical and environmental risk factors that in previous studies have been associated with a higher risk of developing PD, and Table 2 shows the results of univariate logistic analyzes of protective factors frequently associated with a lower risk of developing PD. The relative risk estimates revealed that a higher risk of developing PD was significantly associated with family history of PD, personal history of diabetes, the number of head trauma, the number of general anesthesia received, organic solvents exposure and number of years of organic solvents exposure. Due to head trauma may be associated with reverse causality bias, only head trauma occurring 10 or more years before the diagnosis of PD were considered in the analyzes. In the case of controls, only trauma that preceded 10 years to the age of diagnosis of their respective peers with PD were considered. In this study, none of the factors that are considered protective for the development of PD had a significant association (Table 2). Table 3 summarizes the risk factors associated with Parkinson's disease resulting from the univariate logistic regression analysis.

Multiple logistic regression

In the conditional multiple logistic regression analyzes, a model was created (Table 4) that included the following variables: family history of PD (OR = 5.84) and number of years of solvents exposure (OR = 1.05). Variables that were not significant were not included in the model.

As mentioned in the background, having a history of smoking or consuming coffee has been shown to be associated with a lower risk of developing PD. Although in the present study neither of these two variables were associated with a reduced risk of developing Parkinson's disease, two multiple logistic regression models were made with the variables that were associated with a higher risk of PD but adjusting for the history of smoking and caffeine consumption (Table 5). Making this adjustment, in both models having a relative with PD and the number of years of exposure to solvents were maintained as risk factors.

Discussion

Various epidemiological studies reinforce the hypothesis that PD is a neurodegenerative disorder of

Table 1. Estimation of the association of clinical and environmental factors with the risk of PD resulting from the univariate logistic regression analysis

Variable	OR	CI (95%)	p
Clinical risk factors			
Family history of PD	5.28	2.00-13.95	0.001
Family history of essential tremor	0.65	0.24-1.67	0.37
Diabetes	2.35	1.15-4.81	0.01
Head trauma	1.43	0.82-2.49	0.20
Number of head trauma	1.35	1.03-1.77	0.02
Unconsciousness due to head trauma	1.87	0.77-4.55	0.16
Number of times of unconsciousness due to head trauma	1.53	0.75-3.10	0.23
Personal history of receiving general anesthesia	1.58	0.90-2.75	0.10
Number of general anesthesia received	1.27	1.00-1.61	0.050
Environmental risk factors			
Solvents exposure	2.73	1.13-6.58	0.02
Number of years of solvents exposure	1.05	1.00-1.09	0.01
Pesticides exposure	0.90	0.51-1.80	0.96
Number of years of pesticides exposure	1.01	0.98-1.03	0.31
Herbicides exposure	1.68	0.78-3.62	0.18
Number of years of herbicides exposure	1.03	0.98-1.07	0.19
Well water consumption	0.65	0.37-1.14	0.13

PD: Parkinson's disease OR: odds ratio CI: confidence interval.

Table 2. Estimation of the association of protective factors with the risk of PD resulting from the univariate logistic regression analysis

Protection factors			
Variable	**OR**	**CI (95%)**	**p**
Smoking	0.86	0.48-1.54	0.61
Number of years of smoking	0.98	0.96-1.01	0.27
Caffeine consumption	0.94	0.54-1.63	0.82
Number years of caffeine consumption	1.00	0.98-1.01	0.84
Physical activity	1.53	0.84-2.80	0.16

PD: Parkinson's disease OR: odds ratio CI: confidence Interval.

multifactorial origin, which results from a complex interaction between the genetic characteristics of individuals, the chronic degenerative pathologies they suffer from, various habits, and multiple environmental factors, which can increase or reduce the risk of Parkinson[2,3,5].

Table 3. Summary of risk factors associated with PD resulting from the univariate logistic regression analysis

Variable	OR	CI (95%)	p
Family history of PD	5.28	2.00-13.95	0.001
Diabetes	2.35	1.15-4.81	0.01
Number of head trauma	1.35	1.03-1.77	0.02
Number of general anesthesia received	1.27	1.00-1.61	0.050
Solvents exposure	2.73	1.13-6.58	0.02
Number of years of solvents exposure	1.05	1.00-1.09	0.01

PD: Parkinson's disease OR: odds ratio CI: confidence interval.

Table 4. Multiple logistic regression model of the association of risk factors with the presence of PD

Variable	OR	CI (95%)	p
Family history of PD	5.83	2.18-15.54	0.000
Number of years of solvents exposure	1.05	1.01-1.10	0.008

PD: Parkinson's disease OR: odds ratio CI: confidence interval.

Table 5. Multiple logistic regression model of the factors associated with a higher risk of PD adjusted for tobacco and coffee consumption

Variable	OR	CI (95%)	p
Family history of PD	5.75	2.15-15.36	0.000
Number of years of solvents exposure	1.05	1.01-1.10	0.008

PD: Parkinson's disease OR: odds ratio CI: confidence interval.

Family history of Parkinson's disease

Having a family history PD was associated with a 5.28 times higher risk of PD, which was approximately 1.6 times higher than the risk reported in other studies in various parts of the world[6,17,18] but six times lower than the risk of a study conducted in Italy[5]. A study in Cuba reported an odds ratio of 7.22, being 1.3 times higher than that reported in our study[19].

In the multivariate analyzes, having a relative with PD remained a risk factor for developing PD with an OR of 5.83, which is approximately three and seven times

lower compared to the multivariate analyzes of studies carried out in India (OR: 21.40) and Italy (OR: 41.70) respectively[5,9].

In the meta-analysis by Noyce et al., which added 26 case-control studies, reported a significant association between having a first-degree relative with PD and the risk of developing the disease, with a pooled odds ratio of 3.23 (95% CI 2.65-3.93)[20], which is approximately half the risk reported in our study.

Solvents exposure

Solvents are substances found in fuels, paints, glues, lubricants, degreasers, and cleaning products, all of which have been linked to an increased risk of PD, in part due to anecdotal reports of parkinsonism in people highly exposed to solvents[21].

The association between solvents and the development of PD has been studied mostly in epidemiological studies of the case-control type[22]. Most of the relative risk estimates are reported in a range of 1.0 to 1.8, but in these studies the solvents were treated, as in our study, as a single entity without distinguishing the chemicals[10,22-25]. In general, the observed associations of PD with solvents have been modest and very similar to those reported in our work, and apparently, there are only reports of univariate analysis.

The only study to date that has evaluated the association between PD and exposure to different types of organic solvents present in chemical products is a case-control study conducted with 99 pairs of twins (49 monozygotic and 50 heterozygotes), where for each pair one had Parkinson's disease and the other did not, finding that the most suggestive solvents as possible etiological agents were trichlorethylene (TCE), perchlorethylene (PERC) and carbon tetrachloride (CCl4)[21]. A significantly higher risk of PE was associated with trichlorethylene exposure (OR = 6.1, 95% CI: 1.2-33; p = 0.034), while perchlorethylene exposure (OR = 10.5, 95% CI 0.97-113, p = 0.053;) and carbon tetrachloride (RM = 2.3, 95% CI 0.9-6.1, p = 0.088) had tendencies to be significant. However, the risk estimates were based on a very small number of exposed subjects[22]. TCE, PERC, and CCl4 have been used extensively around the world for decades. TCE has been used as a degreasing, cleaning agent, additive in many common household products, including correction fluid for typewriters, adhesives, paints and carpet cleaners, and stain removers[21].

For future studies, we suggest identifying frequently used chemicals in our country that contain some of the possible etiological agents associated with the development of PD. We also recommend the use of protection in people exposed to this class of substances.

Personal history of diabetes mellitus

In the present study, a 2.35 times higher risk of developing PD was found when the participants had a history of diabetes, which is higher than the study by Schernhammer et al. who found a 1.33 higher risk of PD and is contradictory with the study by Powers et al., who reported that diabetes is a protective factor[8,26].

Traumatic brain injuries

In the univariate analysis, we found a 1.3 times higher risk of developing PD associated with the number of times they received head trauma (one or more times), which is consistent with two similar studies with multivariate analyzes. In the Goldman's study, it is reported that people who have received one head injury had a 2.8 times greater risk of developing PD. While Gao's study was found a risk similar to the present study, with an odds ratio of 1.40 when the subjects had received a single head trauma and an OR of 2.33 when they had received two or more head trauma[27,28]. No univariate analysis reports were found.

Postural instability, stiffness, and bradykinesia are diagnostic criteria for PD and, naturally, the presence of these motor symptoms can cause falls in patients, reporting that up to 90% have fallen at least once[29]. Consequently, studies evaluating head trauma as a risk factor for developing PD will only consider trauma before the onset of motor symptoms of the disease, since failure to do so could incur a reverse causality bias by including in the analysis of head trauma that occurred as a consequence of the early motor disorders of PD[6,29-31]. In a nested casecontrol study carried out with 24,412 people with a diagnosis of PD and 243,363 controls, an increase in the risk of falls was found up to 10 years before the diagnosis of PD[32]. which could cause head trauma. Finally, studies that seek to establish whether head injuries represent a risk factor for the development of PD should eliminate head trauma that occurred 10 years before the diagnosis of the disease.

General anesthesia

In the univariate analysis, a 1.2 times higher risk of developing PD was found associated with the number of general anesthesia received (one or more times), which agrees with De Michele's univariate analysis,

which reported an odds ratio of 1.05, while Zorzon in their multivariate analysis reported a odds ratio of 2.2[5,33].

General anesthesia has been suggested as a risk factor associated with Parkinson's disease in some case-control studies, but not all[5,34]. A meta-analysis with 6 case-control studies found no association of general anesthesia with Parkinson's disease[20]. In a retrospective cohort study that included 490,156 anesthesiologists and 499,388 internists, anesthesiologists were found to have a higher risk of dying from Parkinson's disease than internists.[7] In experimental models, mechanisms have been described that relate exposure to anesthetic gases such as halothane, isoflurane, and nitrous oxide with the development of PD[35].

Study limitations

Due to the coronavirus pandemic (COVID-19) it was not possible to reach the sample size (n = 100). The small sample size of the cases (n = 86) reduces the power of the statistical analyses. To compensate for the above, in some cases two controls were used for each one, which is recommended by Gail, using the case saving rule. Therefore, it is suggested to increase the sample size for future studies[36].

Epidemiological case-control studies have been used successfully to investigate possible associations between various variables and the risk of developing certain multifactorial diseases, such as PD. However, they have biases inherent in their methodology, such as memory bias in elderly patients and reverse causality by not considering that the possible factors associated with PD could be a consequence and not a cause of the disease. In addition, another potential source of bias in this type of study is related to the collection of data in the interviews, where the interviewers, knowing the hypotheses, can, consciously or not, influence the interviewees to provide answers consistent with those hypotheses.

It is necessary to reach a consensus regarding the methodology of epidemiological studies of risk and protective factors associated with PD, to avoid or reduce biases. For greater veracity in future studies, it is suggested to increase the sample size. If feasible, the intensity and duration of the factors associated with PD should be estimated, such as exposure to pesticides and organic solvents, tobacco, and caffeine consumption. Likewise, to reduce the reverse causality bias, only factors before the onset of the prodromal phase of PD should be considered, which is conservatively estimated to begin about 10 years before diagnosis, so this value could be used as a point cut-off point[11].

Conclusions

The findings of this research indicate that the inhabitants of the state of Yucatan are exposed to the following risk factors for developing PD: family history of PD, personal history of diabetes, the number of head trauma, exposure to solvents organics, number of years of exposure to organic solvents, and the number of general anesthesia received. It is necessary to reach a consensus regarding the methodology of epidemiological studies of risk and protective factors associated with PD, to avoid or reduce biases.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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