MEX-PD: A National Network for the Epidemiological & Genetic Research of Parkinson's Disease

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Abstract

Background

Parkinson's Disease (PD) has a complex etiology, involving genetic and environmental factors. Most of our current understanding of the disease comes from studies in populations with mostly European ancestry, representing challenges in generalizing findings to other populations with different genetic, social, and environmental contexts. There are scarce studies focused in Latin American populations. The Mexican population is genetically diverse because its admixture from Native American, European, and African ancestries, coupled with the unique environmental conditions, stressing the relevance of establishing genetic studies in this population. Thus, we have established the *Mexican Parkinson's Research Network* (MEX-PD), a consortium to research the clinical, genetical, environmental, and neurophysiological bases of the phenotypic diversity in Mexican PD patients.

Objectives

Describing how MEX-PD was established, the methods and instruments and presenting the first results.

Methods

Patients and controls were recruited from medical centers in 20 states of Mexico. Initial recruitment included neurological evaluation, cognitive assessment, and DNA collection.

Results

MEX-PD has registered 302 controls and 262 PD patients with a mean age of diagnosis of 61 years (SD=10.86). There were 19.8% PD patients identified with early onset. Levodopa was the most common pharmacological treatment.

Conclusions

MEX-PD contributes to understand PD nationally. The information gathered here will allow us to understand the prevalence of mental health, neurological symptoms, and cognitive function in the PD Mexican population and how genetical and environmental

factors contributes to those outcomes. These will advocate for personalized treatments and improving quality of life in the Mexican population.

Keywords

Parkinson Disease, Epidemiology, MEX-PD, Mexico, Neurology, Movement disorders.

Introduction

Parkinson Disease (PD) is the second most prevalent neurodegenerative disease globally (1). The World Health Organization estimates that over 5.8 million people are affected. This disease, stemming from the loss of dopaminergic neurons in the Substantia Nigra (SN) of the brain stem, is also linked to the intraneuronal accumulation of α-synuclein proteins (2,3).

Given its primary symptoms, such as rest tremor, rigidity, postural instability, and bradykinesia, PD is classified as a movement disorder (3). Nevertheless, it also presents non-motor symptoms, including hyposmia, apathy, anxiety, depression, sleep disorders (like insomnia or daytime sleepiness), mild cognitive impairment (MCI), and dementia (4). These symptoms, varying in presence and severity, contribute to the disease's heterogeneity (5).

Despite the clinical work at large health centers in the largest Mexican cities and efforts from biomedical researchers in the country, there is a need for increasing the research on genetic and environmental risk factors for PD in the Mexican population. To our knowledge, no national epidemiological PD study exists in Mexico to help identify these risk factors, mainly due to the economic and logistic complexity of such an effort. The incidence density of PD in Mexico is estimated to be 9.48 per 100,000 person-years for individuals aged over 20 years old (6,7). It is anticipated that by 2023, this incidence will rise to 14.9 per 100,000 (8), but as yet, no study has confirmed this projection. The highest incidence rates are reported in the states of Sinaloa (27.6 per 100,000), Colima (23.5 per 100,000), and Durango (20 per 100,000)(6,8).

A previous study in the Mexican population identified the rs1491942 variant in the *LRRK2* gene as a risk factor for PD development (OR=2.26, p=0.01), particularly among patients with a high proportion of Native American ancestry (≥56.6%; 9). Additionally, the rs1801133 variant in the *MTHFR* gene was more common in PD patients with 32-52% Native American ancestry compared to controls (OR=2.02, p=0.043; 9). This SNP

has only been reported in the Mexican population, suggesting specific genetic factors may influence PD incidence in this demographic group.

Despite these valuable insights, the epidemiological information regarding the Mexican population remains limited. Mexico has yet to conduct a genome-wide association study (GWAS) or similar large-scale genetic research on PD. Hence, there is a pressing need to understand how genetics contribute to PD and interact with environmental factors in highly admixed populations. The Mexican population, an admixture deriving from Native American (37-49%), European (50-60%), and African (1-3%) ancestries (10,11), presents a unique opportunity for this study.

In response to this need, the Mexican Parkinson's Research Network (MEX-PD; Red Mexicana de Investigación en Parkinson) was established in 2021. This national research consortium brings together experts in genetics, human cognition, functional neuroimaging, and neurologists specialized in movement disorders. This network aims to investigate the prevalence, clinical and cognitive features, comorbidities, and the evolution of PD in the Mexican population and to identify diagnostic and progression biomarkers based on cognitive, genetic and neuroimaging evaluations. Our findings may extend beyond Mexico, providing valuable insights for comparable groups, such as other Latin American countries and Latinos in the USA. The goal of this manuscript is two-fold: one, to present cohort-based information about MEX-PD and the phenotypical and genotypical information we are collecting, aiming to promote local collaborations to increase our cohort, as well as international collaborations interested in admixed populations; and two, to share our current epidemiological data on PD in the Mexican population.

Methods

Participants

At the time of writing this manuscript November of 2022, our study has enrolled 262 patients with PD and 302 control participants. Controls are recruited from medical

centers (e.g., spouses or caregivers of PD patients without a genetic relationship), public events (such as musical shows and science fairs), and parks. Patients with PD have been recruited through both public and private medical centers in twenty Mexican states (Figure 1). PD diagnosis is confirmed by neurologists specialized in movement disorders, based on the UK Brain Bank Criteria. The inclusion criteria for patients are as follows: a) diagnosis of PD; b) born in Mexico; c) majority of lifetime spent in Mexico; d) at least 45 years old; e) provision of written informed consent. The same criteria, excluding a PD diagnosis, are applied for the control group, supplemented by: f) no consanguineous relationship with individuals with PD; and g) no diagnosis of any neurodegenerative disease. All participants are requested to donate a DNA sample via buccal swab for subsequent genotyping, this procedure is included in the informed consent and explained to participants. In this article we will not address this subject as is beyond the scope of this article, but we aim to identify specific genetic variants for PD in our population.

Institutional support and the necessary infrastructure are provided by the *Universidad Nacional Autónoma de México* (UNAM, may translate as National Autonomous University of Mexico). This research has received approval from the Bioethics Committee of the Institute of Neurobiology at UNAM. Additionally, MEX-PD closely collaborates with the Latin American Research Consortium on the GEnetics of Parkinson's Disease (LARGE-PD; 12), which aims to enhance our understanding of PD in Latin America.

Data collection and procedures

Data collection is conducted online using the Research Electronic Data Capture (REDCap) platform(13,14). REDCap is a secure platform where all survey data are recorded and locally saved on a database server at the National Laboratory of Advanced Scientific Visualization at UNAM; under stringent security protocols. Furthermore, sensitive data is pseudonymized for additional protection.

Instruments

To achieve our objectives, participants respond to an array of questionnaires, scales, psychological instruments, and neuropsychological batteries, all in spanish.

Data collection from participants is divided into three stages. Initially, participants are informed about the aims of the study and sign informed consent forms. They also complete a comprehensive record of their clinical history, anthropometric information, an environmental exposure questionnaire, and complete the Montreal Cognitive Assessment (MoCA; 15) validated in the Mexican population and in spanish (16). A neurologist applies the clinical history for PD patients, the official Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS; 17), the Hoehn-Yahr scale (18), and records PD-related medication prescriptions.

Following the initial data collection session, participants are contacted via telephone. In this second session, they complete a series of instruments related to mental health in spanish: the State-Trait Anxiety Inventory (STAI; 19), State-Trait Depression Inventory (ST-DEP; 20), Parkinson Anxiety Scale (PAS; 21) and Symptom Checklist-90-R (22). STAI, SR-DEP and SCL-90-R are validated for the Mexican Population (19,20,23). The Cognitive Reserve Index Questionnaire(24), measuring cognitive reserve, is also included (spanish version).

In the final session, participants are contacted via video call. This session aims to evaluate cognitive function using a computerized neuropsychological battery in spanish called Creyos (initially known as the Cambridge Brain Sciences; https://creyos.com/features/tasks).

A description of all available questionnaires is provided in Table 1.

Table 1. Questionnaires and instruments.

Clinical assessment	
Movement Disorder Society–Unified Parkinson's Disease Rating Scale (23)	This scale supervises the course of PD and the degree of disability. It explores four areas of the disease: • Part I: non-motor experiences of daily life • Part II: motor experiences of daily life • Part III: motor examination • Part IV: motor complications
Hoehn-Yahr scale (17)	This scale measures the symptoms of PD and the level of disability, it considers stages 1 (less affected) to 5 (greatest disability).
Cognitive assessment	
Montreal Cognitive Assessment (MoCA; 15)	Neuropsychological instrument that measures cognitive function. It detects mild cognitive impairment through the screening of seven domains: attention, concentration, executive functions, memory, language, visuoconstructive, calculation and orientation.
Creyos (Initially called Cambridge Brain Sciences)	Neuropsychological computerized battery which measures four cognitive domains (memory, reasoning, verbal ability and concentration). Tasks: Spatial Span, Token Search, Paired Associates, Polygons, Spatial Planning, Grammatical Reasoning, Feature Match, Double Trouble.
Cognitive Reserve Index Questionnaire (CRIq; 24)	This questionnaire estimates an individual's cognitive reserve through collecting information about the entire adult life. It focuses on three areas: schooling, jobs and leisure activities.
Mental health assessment	

State-Trait Anxiety Inventory (STAI; 18)	It is a self-evaluating inventory that detects the state and trait anxiety symptomatology.
State-Trait Depression Inventory (ST-DEP; 19)	It is a self-evaluating inventory that identifies the state and trait depression symptomatology.
Parkinson Anxiety Scale (PAS; 20)	This scale, specifically for PD patients, measures the persistent, episodic anxiety and avoidance behavior.
Symptom Checklist-90-R (SCL-90-R; 23)	This instrument assesses the state of mental health, through nine scales: somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism.

Statistical analysis

Descriptive variables, such as age, sex, years of education, occurrence of head injury, and ancestry, were compared between control and PD patient groups. The Chi-squared test was employed to determine differences in sex, the presence of a head injury or concussion, and self-reported ancestry as a function of the group. Similarly, the Student's t-test for independent samples was used to evaluate differences between groups in terms of age and years of education.

The clinical data was analyzed as follows. The mean and standard deviation of age of onset and disease duration are reported. The median and the minimum and maximum of the Hoehn and Yahr stage, is also described. To determine if there was a difference in the age of onset of PD in the Mexican population compared to other populations (3,25), the number of patients with late-onset PD (LOPD; >51 years) and early-onset PD (EOPD; <50 years) was compared using the Chi-squared test. To detect association

between disease duration and disease severity, as indicated by the Hoehn and Yahr stage, a Spearman correlation was performed.

Moreover, the frequency of initial motor symptoms, the location of the initial motor symptom, pharmacological treatment, and the years of delay in diagnosis among patients were compared using the Chi-squared test. Based on the understanding that pharmacological treatment changes as a function of age and disorder progression (26), it was examined whether the pharmacological treatment in our population was associated with age (segmented into five groups: younger than 45, then divided every 10 years of age, and aged 76 and older), or disease severity (segmented into two groups, divided between those at stage 3 or less and those at stage 4 or more on the Hoehn and Yahr scale), by performing a Chi-squared test. For all analyses, results yielding a p-value of less than 0.05 were considered statistically significant.

All the statistical analyses were performed with the *jamovi* (version 2.3) program.

Results

Demographic data

As of this writing, our study includes 302 subjects serving as controls (81 men and 221 women) and 262 participants with PD (146 men and 116 women). A higher proportion of men than women are represented within the PD group, while in the control group the opposite happened (Table 2). With respect to age, years of education, and the incidence of head injury or concussion, no significant differences were found between the control and PD patient groups ($p>0.05$; Table 2). However, a notable divergence was found in self-reported ancestry between the two groups, particularly concerning Native American and admixed ancestry. PD cases reported Amerindian ancestry more frequently and admixed ancestry less frequently compared to controls ($p=0.0005$). Subsequent recruitment will aim at improving recruiting of controls with comparable demographics of the patients.

Table 2. Descriptive data of the sample. Significant results are marked in bold.

	Controls	**PD cases**	***p***
n Men (%) Women (%)	302 81 (27%) 221 (73%)	262 146 (56%) 116 (44%)	**<0.0001**[a]
Age[b]	58 ± 9.58	68 ± 10.29	0.25
Years of education[b]	14.35 ± 5.31	12.27 ± 5.98	0.09
Head injury or concussion[c] No Yes	 208 51	 153 31	0.45
Participant-reported ancestry[d]	-Amerindian (13.7%) -European (5.7%) -Other (1.6%) -Mixed (79%) • Amerindian and European (94.9%) • Amerindian and Asian (0.84%) • Other (4.26%)	-Amerindian (37.5%)* -European (10%) -Other (0.4%) -Mixed (48.3%)* • Amerindian and European (80.2%) • Amerindian and Asian (2.4%) • Other (17.4%)	**0.0005**

[a]Group x Sex Chi square (2X2); significant differences were observed among all subgroups; *n* and percentage are reported.

[b]Student's t-test; Mean ± standard deviation is reported.

[c]Group x No/Yes Chi square (2x2); *n* is reported

[d]Group x Self-reported ancestry Chi square (2x4); percentage is reported; differences between No PD vs. PD patients*$p<0.001$

The geographical distribution of participants by state is illustrated in Figure 1. The states contributing the most participants were located in the central region of the country, specifically Mexico City, San Luis Potosí, and Michoacán. Similarly, for the control group, the states with the greatest representation were also located in the central region, with most participants hailing from Mexico City, Querétaro, and Michoacán.

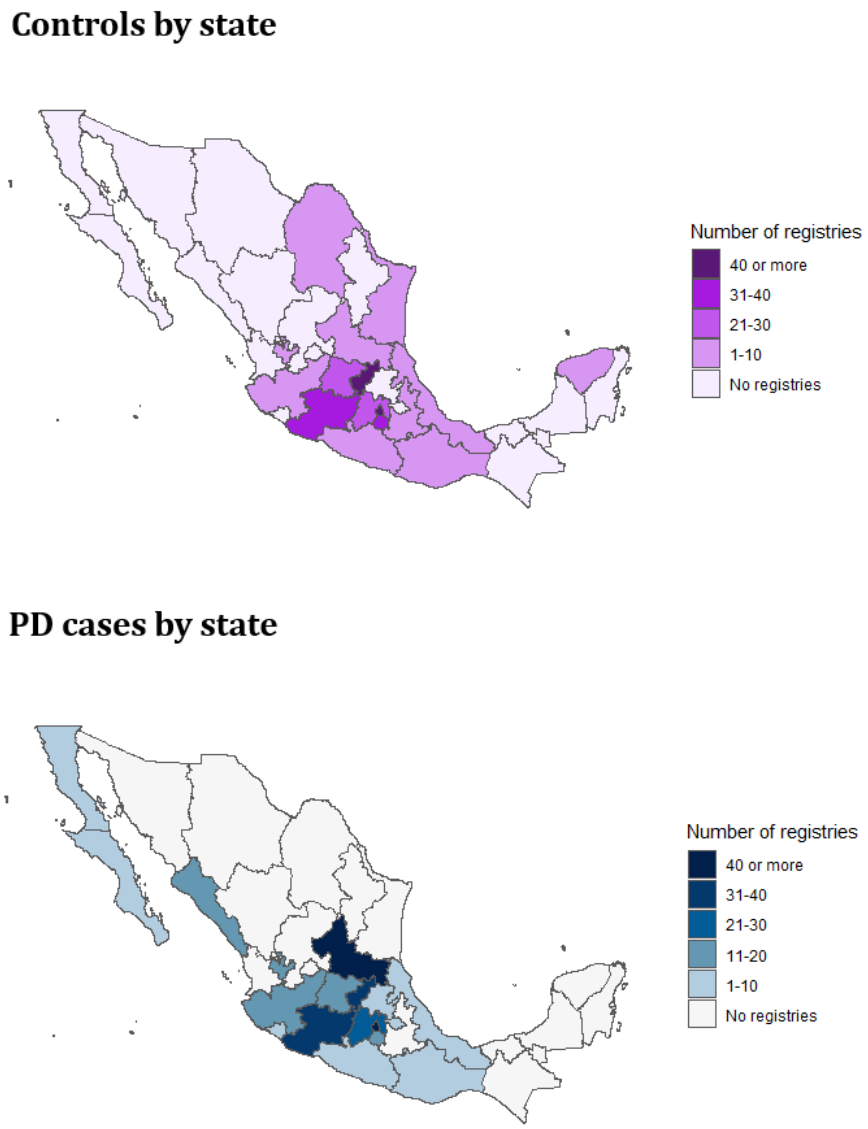

Figure 1. Maps of Mexico with the geographical distribution of participants by state.

Clinical data

The clinical characteristics of the patients are presented in Table 3. The average age at diagnosis was 61 years (standard deviation [SD] 10.86), with a mean disease duration of 6 years (SD 5.38). Our sample comprised 19.8% Early Onset Parkinson's Disease (EOPD) patients and 80.2% Late Onset Parkinson's Disease (LOPD) patients.

At the time of their initial interview for this research, most patients were in a mild state of disease progression, as indicated by a median Hoehn & Yahr stage of 2 (min-max 1-5). A modest direct correlation was observed between disease duration and grade of disability ($r= 0.26$, $p<0.0001$, $r^2=0.068$).

Regarding pharmacological treatment, we found that 92.5% of PD patients were prescribed levodopa (either alone or in conjunction with a dopaminergic agonist), while 7.5% were undergoing other forms of pharmacological treatment (Table 3).

Table 3. Clinical characteristics of the whole PD patient's sample.

		p
Age at onset (years)[a]	61 ± 10.86	
50 years or less (EOPD)	19.8%	**<0.0001**
51 years or more (LOPD)	80.2%	
Disease duration (years)[b]	6 ± 5.38	
EOPD[c]	8 (0-28)	**<0.001**
LOPD[c]	5 (0-22)	
Hoehn and Yahr stage[d]	2 (1-5)	
EOPD	2 (1-3)	**0.038**
LOPD	2 (1-5)	
Initial motor symptoms (n)[e]		
Tremor (138)	52.7%	
Postural instability (16)	6.1%	
Tremor and instability (31)	11.8%	**<0.0001**
Other (77)	29.4%	
EOPD[e]		
Tremor	43.5%	
Postural instability	8.7%	
Tremor and instability	6.5%	**0.0002**
Other	41.3%	
LOPD[e]		
Tremor	61.9%	
Postural instability	5.4%	

Tremor and instability Other	12.0% 20.7%	**<0.0001**
Pharmacological treatment[f] Dopamine agonist therapy (DA)	5%	**<0.0001**
Levodopa therapy	40.6%	
DA+Levodopa therapy	51.9%	
Other therapy	2.5%	

[a]EOPD vs LOPD Chi square; significant differences were observed. p<0.001; mean ± standard deviation is reported.

[b]Mean ± standard deviation is reported.

[c]Median (Min-Max) is reported; U Mann-Whitney between disease duration and age at onset were made. p<0.001.

[d]Median (Min-Max) is reported; Spearman correlation between disease duration and Hoehn and Yahr were made. p<0.001; U Mann-Whitney between Hoehn and Yahr and age at onset were made. p=0.038

[e]Type of initial motor symptom (4x1) Chi square; differences were observed. p<0.001; n and % is reported.

[f]Type of pharmacological treatment (4x1) Chi square; differences were observed. p<0.001; % is reported.

There was a borderline association between the frequency of pharmacological treatment and etarian group (p=0.058; Figure 2.A). A subsequent analysis, which only included the most common treatments in the sample (DA+Levodopa and Levodopa alone), did not show a significant association (p=0.43). Additionally, we analyzed the association between the type of pharmacological treatment (limited to DA+Levodopa and Levodopa alone) and disease severity, but no significant association was found (p= 0.43; Figure 2.B).

On the other hand, regarding the initial motor symptoms, tremor was the most common (52.7%, *p*<0.0001); and the symptoms occurred mainly in the upper limbs (58.1%, *p* <0.0001; Figure 2.C).

Finally, Figure 2.D describes the years of delay in the diagnosis of PD with respect to the time when the motor symptoms began. The majority (47%) of the patients were diagnosed the same year that the motor symptoms began ($p<0.0001$), while 34% were diagnosed between the first and second year and 19% were diagnosed after three years or more.

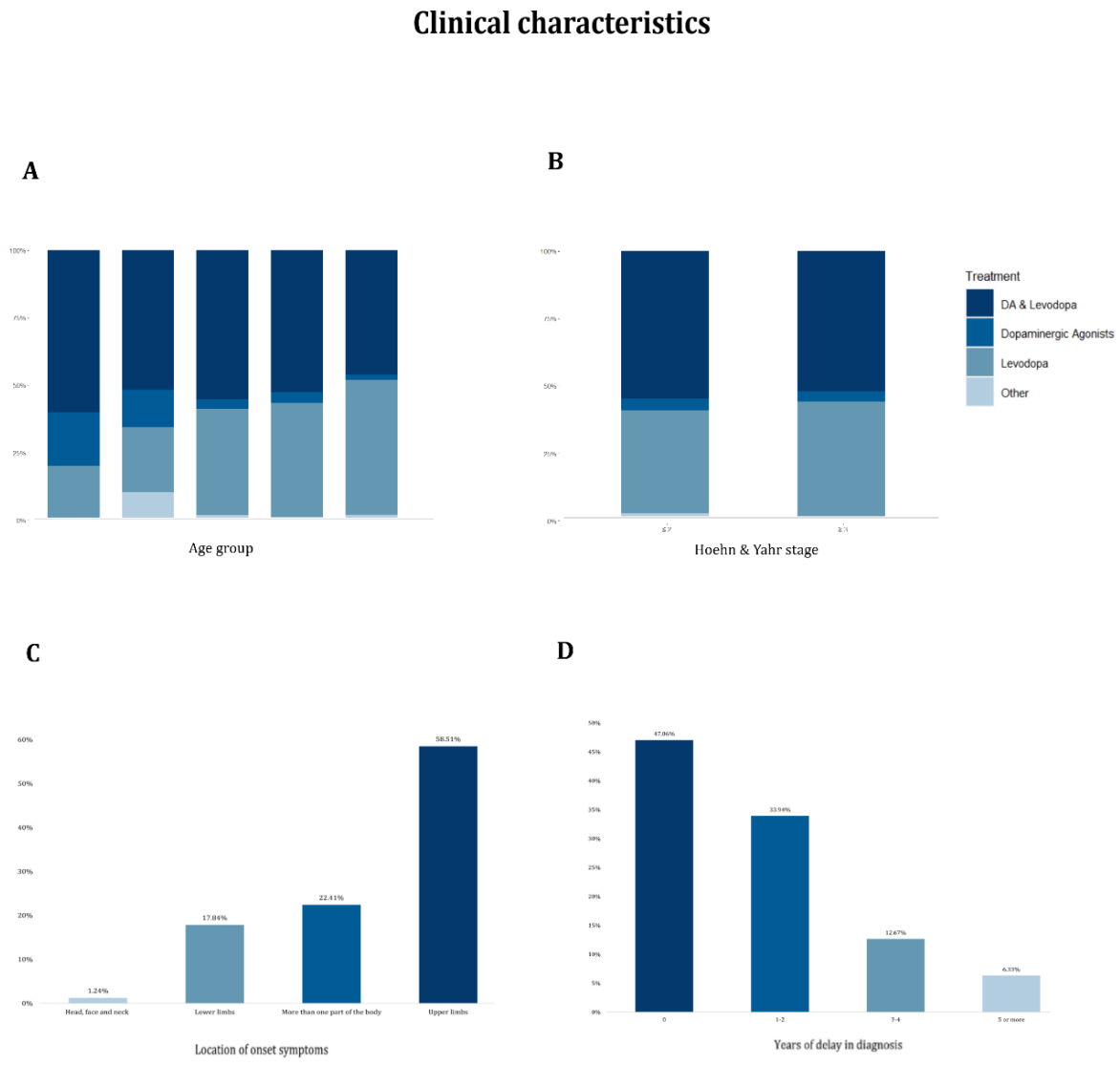

Figure 2. Frequency of pharmacological treatment: Dopaminergic agonists (DA) and levodopa and other as a function of age group (A) and HY stage (B). There was no difference of treatment as a function of age (A) or stage (B; $p>0.05$). Percentage of patients by the location of the initial symptoms (C). Years of delay in the diagnosis (D).

Discussion

MEX-PD is an effort to compile epidemiological data from PD patients throughout Mexico, to identify how the genetic and environmental factors impact the presence and progression of PD in the Mexican population. We want to understand if the genetic admixture and the unique environmental conditions in Mexico might have a differential impact with respect to other populations.

Currently, we have data from 20 states (62.5% of the Mexico states) within the national territory. As it was shown, in this Mexican cohort, the number of men was significantly higher (56%, Table 2) than women (44%) in the PD group, which is consistent with other populations(27,28). However, we have an opposite pattern for the control group: there are more women than men, thus, we will focus on registering more men in the next waves of the study. Regarding the dispersion of the records throughout the country, we can observe that most of them are located in the central part of Mexico, therefore, an effort will be made to register more patients and controls from the north and south-east of Mexico. Regarding this fact, there is a need to have more movement disorder specialists in every state of our country.

As part of the study, we asked the participants to self-report the type of ancestry. We observed that patients self-identify more as Amerindians (37%) and less as mixed (48.3%) compared with controls (13.7% and 37.5% respectively). This might suggest that patients could come from different regions of the country where is more frequent some kind of ancestry, for example, places where there are people with native american ancestry. This information highlights the relevance to analyze genetic data in order to detect if ancestries could play a role in the probability to develop PD.

On the other hand, evidence suggests that trauma is a risk factor for the appearance of PD (29), although results are controversial (4,30). In our cohort, the differences about head injury or concussion between groups were not significant, suggesting head trauma

is not a clear risk factor for PD in our population. However, this result should be taken as preliminary, expecting to assess this factor in a larger sample size to be collected in later waves.

The age of onset of our sample was 61 years old (SD 10.86), which is consistent with most populations (27,31). In a previous study reported by the National Institute of Neurology and Neurosurgery (NINN), located in Mexico City, the age of onset of PD was 57 years (6). However, that report did not mention from which state of the country the patients came from. The difference in age of onset between studies could reveal how genetics or environmental factors, or their interaction, plays a role in the PD onset. Another potential factor that might explain the age of onset difference is the fact that the previous work obtained data only from the NINN, while the effort of MEX-PD is trying to incorporate data reaching all the states of the country; still now our study includes individuals in 62.5% of the national territory.

Interestingly, the percentage of EOPD patients in our sample is 19.8%. Our data suggests that the Mexican population has a large proportion of EOPD compared with Europeans (5-15%) (3,25). However, in the posterior waves we will be able to analyze statistically if the EOPD in the Mexican population is more frequent than other populations, and if it is possible that specific genetic variants might be associated with the age of onset in our cohort.

Regarding the time elapsed between the appearance of the first symptoms and the diagnosis of PD (Figure 4), we can see that 47% were diagnosed the same year that the symptoms began, while 34% took between one and two years, and 19% took more than three years to be diagnosed. This information is relevant given that the longer the patient takes to be diagnosed, affects the estimates of the presence of the disease in the country population.

The pharmacological treatment that most of the patients received is levodopa (92%), followed by dopamine agonists (DA) (40.6%). It has been reported that DA are mostly

prescribed in people younger than 60 years because it helps to avoid motor complications caused by levodopa use (26). In fact, our data shows a trend that the use of DA decreases with age and levodopa increases, but the treatments were not associated with symptoms severity either.

About motor symptoms, half of patients (52.7%) had tremor as a first initial symptom, while 11.8% also had postural instability, and even this prevalence is maintained among EOPD and LOPD. Besides, these symptoms appeared mostly in the upper limbs. This initial symptomatology is consistent with what has been reported in other studies (32).

This work aims in the future to deepen our understanding of PD in the Mexican population, advocating for personalized treatments and improving patient outcomes in the Mexican population.

Limitations

A limitation of this study is the lack of longitudinal follow-up of patients to evaluate the motor and non-motor symptoms progress. Moreover, our sample is highly concentrated at the center of the country, with a greater number of women in the control group and younger than the patients group. To manage this, we are making an effort to recollect more information from the north and south-east of the country, as well as register older people and more men for the control group.

Future directions

Genetic analysis

One of the aims of Mex-PD is the genetic characterization of Mexican individuals with PD. This will be done through DNA collection and posterior genotyping, driven by the support and collaboration with Global Parkinson's Genetics Program (GP2) (33) and LARGE-PD (12).This knowledge will allow us to identify PD risk variants in our population, as well as to perform bioinformatic analysis such as the Polygenic Risk Score (PRS) associated with the symptoms.

Neuroimaging

Patients and controls will be invited to attend the National Laboratory for Magnetic Resonance Imaging at UNAM campus Juriquilla in Queretaro city, to participate in an MRI session. This session will include *state-of-the-art* resting state functional imaging and high resolution multicontrast structural acquisitions in a 3T scanner, including T1, T2, (multishell) diffusion and neuromelanin weighted imaging. We expect to characterize the main functional and structural brain properties of patients with PD, aiming at identifying diagnostic and progression biomarkers for the disease and its non-motor symptoms.

Mental health and Cognitive analysis

The presence of mental health problems and cognitive impairment can affect the quality of life PD patients. As part of the evaluation of non-motor symptoms, the presence of anxiety and depression (state and trait) will be described. Also, global cognitive function will also be assessed to differentiate those with MCI. Moreover, we plan to evaluate different cognitive domains to find out which are the most affected in people with PD, and in this way future neuropsychological interventions will focus on these domains.

The results obtained from mental health and cognitive function will be compared between controls and patients, as well as their correlation with genetic data, structural and functional properties of the brain and environmental characterization.

Social community work

To engage with the community, we have established links with some Parkinson's disease patient support groups through our Facebook page (https://www.facebook.com/RedMEXPD). We have organized webinars with neurologists and movement disorders specialists, published infographics related to PD and promoted training or events related to PD.

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Funding Sources for study

MEX-PD thanks the support from the American Parkinson's Disease Association through a Diversity in Parkinson's Disease Research Grant (APDA/D07). MER thanks fellowship support from the Rebecca L Cooper Medical Research Foundation (F20231230).

IFM and MIM are supported by the National Institutes of Health (NIH) (R01 1R01NS112499-01A1), ASAP-GP2 and the Parkinson's Foundation.

Subaward LARGE-PD MJFF

PAPIIT-DGAPA-UNAM IN208622 to SA. PAPIIT-DGAPA-UNAM IN217221 to AERC. This project was supported by CONAHCYT-FORDECYT-PRONACES grant no. [11311] and [6390]. AMR was supported by Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica–Universidad Nacional Autónoma de México (PAPIIT-UNAM) grant no. IN218023.

ALF is a doctoral student of the *Programa de Doctorado en Psicología de la Universidad Nacional Autónoma de México* and she is a scholarship holder who received a grant scholarship (1222481) from CONAHCYT for her Psychology PhD studies.

PRP is supported by the GP2 Trainee Network, which is part of the Global Parkinson's Genetics Program and funded by the Aligning Science Across Parkinson's (ASAP) initiative.

Acknowledgments

This work received support from Luis Aguilar, Alejandro León, and Jair García of the Laboratorio Nacional de Visualización Científica Avanzada. We thank Carina Uribe Díaz, and Alejandra Castillo Carbajal for their technical support.

We would like to thank the clinical neurologists who have contributed their valuable time and expertise for the recruitment and evaluation of participants: Sara Isaís Millán, Diana Deras, Lucero Ugalde, Omar Cárdenas, Ildefonso Rodríguez, Maritza Valadez, Moíses Rubio, Teresa Pérez. Those that contributed to collecting information and or sample processing from the participants: Roberto Estrella, Ingrid Salazar, Nelly Daniela López, María José Fernández, Alfonso Bravo, Diana Ramírez, E. Ivett Ortega-Mora, Sucel

Iñiguez, Elissa López, Héctor Mederos, Abril Cerón, Brissa Peralta, Antinea Portillo, Itzel Hérnandez, Jonatan Serrano, Alan Morquecho, Jorge Aguilar, Diego Buoker, Itzel Ortiz, Diego Duarte, Karen Alberto, Diana Laura Hernandez, Ana González, Gabriel de Anda, Luis Hernández, Francisco Ramírez

We also thanks support from Mario Nandayapa Quartet, Yoloxochitl Sánchez-Guevara, Instituto de Biotecnología UNAM and Centro Cultural Manuel Gómez Morin, who facilitated recruitment of participants.

Financial Disclosures of all authors

The authors report no competing interests.