VIEWPOINT

Bridging the Gaps: More Inclusive Research Needed to Fully Understand Parkinson's Disease

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Parkinson's disease (PD) research has historically neglected the study of diverse populations, and the field as a whole has suffered as a result. By failing to address PD diagnosis and care in all communities, a tiered PD treatment system has evolved in which certain racial and ethnic populations experience delayed diagnosis and a lack of expert PD care.[1] Clinical trial recruitment in nonwhite populations remains dismally low,[2] which fundamentally impacts the ability of the PD research community to right these wrongs. Research of PD care and clinical differences of women compared with men has also been limited. By focusing almost solely on PD biology in men of European ancestry, PD researchers have been missing the chance to learn about the genetics and molecular biology of PD in other populations. In the slowly growing body of work aimed at diverse populations accomplished to date, information is being uncovered with the potential of improving our understanding of PD as a whole, further underscoring the need to study PD biology in a wide range of underrepresented groups. The American Parkinson Disease Association convened the first-ever Diversity in Parkinson's Disease Research Conference to address the unique and urgent needs surrounding PD in diverse populations and underrepresented communities.[3] With the support of a grant from the Patient-Centered Outcomes Research Institute, experts were gathered to review the current data and to spur conversation among participants about ways to further our understanding of PD in these populations, with the ultimate goal of improving and expanding PD research and services. The 3 main issues identified were delayed diagnosis and lack of expert care, inadequate clinical trial participation, and unexplored biological differences in underrepresented and understudied PD populations

In this Viewpoint, we discuss these problems, present potential solutions, and formulate proposals for future research exploration.

Key Words: diversity, underrepresented populations

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The Problems Identified

Delayed Diagnosis and Lack of Expert Care in Underrepresented PD Populations

There are discrepancies in the natural history and outcomes of PD patients in various underrepresented populations. The available evidence suggests that the incidence and prevalence of PD may not be consistent across all ethnicities. Several studies have suggested that African Americans and Asian Americans may have lower incidence and prevalence than the general population.[4-7] Interestingly, the difference in prevalence was more notable than the difference in incidence, which has been taken as evidence that the disease course of African Americans is shorter and possibly more aggressive.[2] The only door-to-door study of this issue in the United States, conducted nearly 40 years ago in a rural area, ultimately did not show a difference in prevalence between ethnicities, but also found that more than 40% of PD cases were undiagnosed, with twice as many

African Americans found to be undiagnosed as whites.[8] In an autopsy study, the prevalence of incidental Lewy bodies in black Africans was the same as that seen in African Americans, suggesting that rates of PD would be the same as well.[9] On the whole, although these observations raise important questions, the extent and quality of the data are so limited that it remains unclear whether the apparent discrepancies in incidence and prevalence are because of biologic causes or of delayed or missed diagnoses.

There are also important discrepancies in access to care. A study that looked at national data across a wide range of neurologic conditions including PD demonstrated that black participants in the study were 30% less likely to see an outpatient neurologist compared with white participants. Hispanic participants were 40% less likely to see an outpatient neurologist. Black participants were also more likely to be cared for in the emergency department and to have more hospital stays.[10] A study that examined referral rates for neurologic care specifically in PD demonstrated reduced referrals for blacks. Not seeing a neurologist was correlated with increased mortality, hip fractures, and placement in long-term-care facilities.[11] African Americans with PD had lower utilization of outpatient rehabilitation services such as physical and occupational therapy.[12]

In a study at a tertiary movement disorders center, at the time of presentation African Americans showed greater disability and disease severity than white patients and were less likely to be prescribed dopaminergic medications, particularly newer agents.[1] In another study, African Americans were 4 times less likely than whites to receive any PD treatment, even controlling for health care insurance.[13] There is evidence that African Americans present for medical attention at a later stage than whites and are more likely to underreport disability compared with actual motor impairment.[14] Biologic differences may contribute to these discrepancies in disease severity, but social reasons for disparities in PD care must be considered as well. These may include low health literacy, physician bias with fewer referrals to neurology, less patient reporting of disability, or more tolerance for disability among patients.

African Americans are referred for deep brain stimulation (DBS) surgery at lower rates than whites.[15] Different DBS rates may reflect biologic differences between patient populations, with fewer African American patients meeting clinical criteria to be appropriate DBS candidates, such as presence of motor fluctuations or tremor predominance. Social reasons, however, may also play a role in decreased referrals including limited access to care, lack of insurance, mistrust of the health care system, lack of specialists in particular geographic areas, and physician bias with fewer referrals to neurosurgery.

It is important to note that the specific issues identified here are most relevant in the United States, but are examples of a global problem. There are populations throughout the world that lack access to care and are understudied. In addition, there is a wide array of variables that can influence prevalence, natural history, and clinical expression of PD in populations around the world, including genetics, cultural attitudes to chronic disease, and environmental exposures.[16] Economic concerns also play a major role in treatment of PD around the world, with certain treatments unavailable in impoverished areas.

Inadequate Clinical Trial Participation

Trial participation in underrepresented populations across medical disciplines is low, and this is true in PD clinical trials as well. One reason for this may directly relate to delayed diagnosis and lack of expert care as discussed above. If underrepresented patients begin their care with more advanced disease, they will likely be less eligible for trials. Similarly, if underrepresented patients are less likely to be seen by a movement disorders specialist, they are less likely to be referred for trials. In addition, because of historic and societal reasons, there is an unfortunate fear of a lack of confidentiality in clinical trials and a fear of the research process itself.

"Life chaos,"[17] defined as a lack of structure and organization in everyday life with an inability to develop and sustain habits and routines, may play a role in decreased clinical trial enrollment in certain underrepresented populations. Life chaos is linked to low socioeconomic status, which is in turn associated with certain underrepresented populations. Life chaos makes it difficult to participate in research, which requires significant amounts of organization and planning.

Unexplored Biologic Differences

One example of the underexplored biologic heterogeneity among PD populations is in the field of PD genetics. In 2009, 96% of genetic studies only used European data. By 2016, that number decreased to 81%, largely because of the inclusion of more Asian individuals. Genome-wide association studies of PD participants do not mirror the world's population.

In Latinos, there is a huge admixture of African, Amerindian, Asian, and European genes, which varies depending on which country in Latin America is being studied. Studying this complex gene pool has the potential to reveal new PD genes and new mutations in known PD genes.[18] Increased understanding of the genetic variability of PD is vital in the current and future climate of personalized medicine. Underserved populations that are not studied will be at an even further disadvantage in PD treatment if their particular genetic variations are not explored in the development of new therapies. In addition, genetic determinants of PD identified in particular populations, can expand our understanding of PD biology more generally, so it is vital to be as comprehensive as possible in our study.

Women and PD

Fewer women than men are diagnosed with PD, at a ratio of approximately 3 to 2.[19] However, many of the same issues identified in underrepresented racial and ethnic groups, including differences in clinical care, low rates of clinical trial participation, and unexplored biologic variation, hamper our full understanding of PD in women. Referral rates to a neurologist are lower among women PD patients, similar to referral rates among black PD patients.[11] In addition, women as compared with men are less likely to have informal caregiver support (such as a spouse or other family member).[20] Men and women tend to have different motor and nonmotor phenotypes. For example, women have more tremor as a presenting symptom.[21] Cognitive profiles are different as well, with women tending to perform better on tests of overall cognition but worse on visuospatial functioning.[22] Increased research dedicated to further identifying and understanding these differences is crucial.

The Proposed Solutions

Potential solutions to the identified problems are proposed below. The efficacy of each of these suggested solutions requires testing.

Delayed Diagnosis and Lack of Expert Care in Uunderrepresented PD Populations

Suggestions to reduce health care disparities include:

- Development of community education programs, traditional and social media campaigns that educate minority populations on the symptoms of PD.
- Education of primary care physicians about detecting and treating PD.
- Tele-health to expand access to movement disorders expertise.
- Incentivizing health systems to improve their health care disparities.

Inadequate Clinical Trial Participation

Suggestions to increase clinical trial participation include:

- Using patient navigators (PNs) trained to support people through the trial. African American participation in cancer clinical trials increased from 9% to 16 % with PNs.[23]
- Enhancing sensitivity to minority needs by translating study materials, emphasizing that immigration status is not a barrier and will not be documented, creating low health literacy materials, and tailoring educational materials to specific ethnicities.
- Sending recruitment letters that describe the health disparities and explain why participation in research is so important.
- Easing people into trials by having them enroll in an observational trial first before an interventional trial.
- Moving research sites into the community for better access.
- Modeling efforts after the RECRUIT trial,[24] which used trust-based relationships with minority physicians as a way of increasing minority enrollment.
- Integrating social and medical services in the trial process to provide for what people need to allow them to participate in trials.
- Loosening up trial design so that those with life chaos can participate more easily.

Unexplored Biologic Differences

Suggestions to explore biologic differences include:

- Exploration of genetic differences in diverse PD populations can be accomplished by expanding on current studies and modeling the success of current studies in other populations. The Latin American Research Consortium on the Genetics of PD (LARGE-PD) is a network with 32 sites in 12 Latin American countries[25] designed to collect samples and study the genetics of Latin American populations. Approximately 4000 individuals have been recruited (half with PD, half controls). The genetic data are complemented by information collected on environmental exposure, clinical course, and cognitive data. This effort is already reaping benefits such as the identification of the population-specific mutation in the glucocerebrosidase gene, K198E, found in a Colombian cohort.[26] Because genetic information highlighted in one population often has implications for PD more generally, LARGE-PD holds a key to an underexplored treasure trove of PD genetic information.
- Identifying and studying medical comorbidities in underrepresented PD populations.

PD Clinical Care and Research of the Future

Our vision is that PD research of the future will take a multipronged approach to addressing diverse and underrepresented populations. Studies will be conducted to test methods that would disrupt social barriers to PD diagnosis and health care access. Clinical trials will be inclusive and representative of all populations. Biologic differences between populations will be investigated that will provide important new insights and equalize the ability to offer personalized medicine to all. A better understanding of PD for some means a better understanding of PD for all.

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