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Impact of ethnicity on the natural history of Parkinson disease

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Parkinson disease (PD) is a multifactorial and multisystem condition,¹ its heterogeneity manifests in the spread of neurotransmitter involvement, the wide range of evident motor and non-motor symptoms with possible subtypes, and the complex time line of PD, including a prodromal, motor and palliative phase.² PD affects people of all races and ethnicities worldwide. The epidemiology of PD among various ethnic groups has been poorly studied and the data arising have been contradictory, with a suggestion that PD is relatively more frequent in Western populations.^{3,4} However, systematic surveys do not confirm this observation, and local studies have suggested that Asian and African people may express phenotypic variants of PD.⁵⁻⁷ In addition, there have been reports of ethnic variation in the frequency of known PD genes, including leucine-rich repeat kinase 2 (*LRRK2*) and glucocerebrosidase (*GBA*).⁸

As an analogy with other neurological conditions, such as essential tremor,⁹ multiple sclerosis¹⁰ and amyotrophic lateral sclerosis,¹¹ differences between ethnicities have been reported in prevalence, incidence and clinical presentation. Ethnic differences are therefore important to explore, as this might improve awareness of these conditions in underserved communities and address inequalities in health care delivery worldwide.^{12,13}

Our review aims to summarise some key studies emphasising the importance of research investigating ethnicity and PD. We used PubMed to analyse original and review articles, and specialist society publications and guidelines for PD to formulate an evidence-based overview of the topics as applied to clinical practice.

Prevalence of Parkinson disease across different geographical regions and ethnic groups

The origin of PD is thought to be multifactorial, including a combination of important aspects such as genetics and environmental factors (eg, neurotoxins and nutrition).¹⁴ Sociocultural and geographical differences may influence nutrition and environmental issues between different ethnicities. Therefore, it is not surprising that the prevalence of PD has been suggested to vary between different ethnicities across the world. However, the current data are inconclusive and it is challenging to compare epidemiological studies because the applied diagnostic criteria, case ascertainment, sample sizes and methodology vary widely between studies.^{4,15} Further, the varying age distribution, life expectancy and length of survival worldwide might influence the reported differences.^{4,16} These confounding factors have to be taken into consideration when interpreting epidemiological data.¹⁷

The major approaches for epidemiological studies used in the literature are:

- community based;¹⁸
- random cohort sample;¹⁹
- cross-sectional prevalence studies;²⁰
- door-to-door survey;²¹

Summary

- Parkinson disease (PD) affects people of all races and ethnicity worldwide.
- PD is a multineurotransmitter and multisystem disorder and our current concept of the natural history of PD has changed considerably over the past decades.
- Many aspects of this heterogeneous condition still remain unexplained; one aspect that is poorly studied is the role of ethnicity and manifest motor and non-motor PD.
- Some preliminary data suggest that the prodromal risk of developing PD, clinical symptom expression and the experience of living with the condition may vary between different ethnic groups.
- Several factors might play a role in the influence of ethnicity on PD, such as pharmacogenetics, sociocultural aspects and environmental exposures.
- Increased knowledge on the role of ethnicity in PD may help shed light on the symptom expression and treatment response of PD, address inequalities in health care delivery worldwide and improve the delivery of personalised medicine.

- database mining (questionnaires sent out to population);²²
- death certificates;²³
- drug tracer approach (registered levodopa prescriptions);²⁴
- hospital admissions;²⁵
- recipients of health care;²⁶
- record-based general hospital;²⁷ and
- post mortem survey.²⁸

In 2007, Dorsey and colleagues²⁹ estimated that the number of PD cases worldwide is set to double by 2030, of which a large part is related to the improved diagnosis in Asian and African countries. Currently available literature indicates that the prevalence of PD appears to be higher in the Western population compared with Asians and Africans.^{3,4,13} Wright Willis and colleagues³⁰ have conducted a population-based study in Medicare beneficiaries aged over 65 years in the United States and came to the same conclusion that PD is more common in white people (overall age-standardised prevalence, 2168/100 000) compared with black people (1036/100 000) and Asians (1139/100 000).³⁰ In addition, a review by Pringsheim and colleagues¹⁷ analysed door-to-door surveys and random population samples according to geographic location published from 1985 to 2010. Their findings showed that PD prevalence was generally lower in Asia (including India, Taiwan, Hong Kong, Korea, China, Japan, Singapore and Saudi Arabia) compared with North America (Canada), Europe (including France, Italy, Spain, the Netherlands and Germany), Australia and South America (including Brazil, Uruguay, Argentina and Bolivia). The authors found a significant difference for the population aged 70–79 years between Asia (646/100 000) and North America, Europe and Australia (1601/100 000).

However, there is a substantial variability in reporting among the specific studies, even in each country, and several authors have questioned if it can be generalised that the prevalence is lower in Asian compared with Western populations.³¹ As an example, in China, several studies have reported similar PD prevalence compared with Western countries with dominantly white population.³² Surathi and colleagues³³ have argued that, in a diverse country such as India, the prevalence cannot be generalised from small population studies within India.³³ In relation to differences within Europe, a community survey-based study in Europe (EUROPARKINSON Collaborative Study), including France, Italy, the Netherlands and Spain, has concluded that there appear to be no significant differences in PD prevalence among countries in Europe in spite of environmental differences.¹⁵ Therefore, more large scale, multicentre epidemiological studies are needed to ascertain true differences in prevalence.

Most studies agree that the prevalence increases with age irrespective of the ethnic and geographical background.^{15,34,35} There is a clear tendency in an increase of life expectancy across the world, which is likely to lead to a growth in disorders such as PD and, thus, influence a change in the currently reported figures worldwide.^{29,36} Moreover, several researchers have recently suggested a different concept of PD, describing it as a syndromic condition, not as a single disease.^{2,37-39} The syndromic multifocal nature of PD is evident in the phenotypic heterogeneity of PD in various ethnic groups, which we discuss below.

Description of atypical parkinsonism worldwide

In our review, we are considering different terminology. Atypical parkinsonism refers to the atypical presentation of PD, different to other well described types of parkinsonism, such as multiple system atrophy, progressive supranuclear palsy and Lewy body dementia. These atypical forms of parkinsonism are often referred to as unclassifiable atypical parkinsonism. There are several descriptions of these atypical presentations worldwide which appear to vary between different ethnic groups and, therefore, it is an important aspect when discussing ethnic differences in parkinsonism. Further, understanding of these unclassifiable atypical parkinsonisms may help to better understand variations between idiopathic PD in the future.

An occurrence of a three- to four-fold increase in the frequency of atypical parkinsonism was reported in Afro-Caribbean and Indian ethnic minorities living in the United Kingdom.⁵ These atypical features, characterised mainly by levodopa hypo-responsiveness, bradykinesia dominance and early cognitive dysfunction, were noticed even after the exclusion of clinically probable multiple system atrophy, progressive supranuclear palsy and Lewy body dementia. Chaudhuri and colleagues⁵ acknowledged that, although the observation could only be validated with post mortem confirmation, it may nevertheless indicate increased susceptibility of these ethnic groups to atypical parkinsonism, secondary to different genetic make-ups and environmental exposure before migration. The findings were later further analysed through imaging studies by subjecting the same cohort to magnetic resonance imaging and ¹⁸F-fluorodeoxyglucose and ¹⁸F-fluorodopa positron emission tomography of the brain.⁴⁰ In spite of the atypical clinical presentation, the analysis showed no difference between atypical and typical parkinsonism groups and was suggestive of a pattern of idiopathic PD.

Similar findings were also reported in the French West Indies population, where researchers and health professionals found a clinical presentation of an atypical parkinsonism that could not be

classified as multiple system atrophy, progressive supranuclear palsy or Lewy body dementia among local non-white patients.^{6,41} Reports from Guadeloupe describe a high prevalence (around two-thirds) of atypical parkinsonism with levodopa hypo-responsiveness.⁶ The phenotype was further characterised by bradykinesia and rigidity dominance and absence of levodopa peak-dose dyskinesia.⁶

It has been speculated that an environmental neurotoxic origin, which may be associated with the increased consumption of tropical teas and fruits of the Annonaceae family,^{6,42} may be one of the main underlying risk factors for the high prevalence of atypical forms of parkinsonism.

Worldwide, there are examples of atypical forms of parkinsonism most likely due to an environmental factor. In Guam, for instance, there were reports of an exceptional high prevalence of an “overlap” syndrome presenting with parkinsonism and motor neuron disease and/or dementia. In 1956, this unclassifiable parkinsonism was titled amyotrophic lateral sclerosis/parkinsonism-dementia complex.⁴³⁻⁴⁶ A similar phenotype has also been reported on the Kii peninsula, in Japan, and Papua, in Indonesia.⁴⁷⁻⁴⁹ Likewise, a one-year study conducted in New Caledonia reported an unusually high prevalence of atypical parkinsonism, described by bradykinesia and rigidity dominance, levodopa unresponsiveness, early dementia with frontal lobe signs and postural disorder.⁵⁰ As a further example, mainly in Eastern Europe, there were reports of another atypical parkinsonian syndrome (characterised by bradykinesia, dysarthria, dystonia, postural impairment and levodopa hypo-responsiveness) that was caused by intravenous use of methcathinone hydrochloride (ephedrone), which contains manganese.⁵¹

Ethnicity and expression of motor and non-motor symptoms in Parkinson disease

Symptom expression in PD is very heterogeneous. Besides motor symptoms, the modern concept of PD encompasses non-motor symptoms (NMS) as one of the main burdens and the key determinants for the quality of life of patients with PD and their carers.⁵² NMS have been increasingly studied during the past decades, and it has been shown that they vary to a large extent among patients, ranging from gastrointestinal and urinary to cognitive problems. At present, there are tools to capture NMS in a holistic manner, such as the patients' self-reported NMS Questionnaire (NMSQuest) or the health professional-completed NMS scale.⁵² The validated NMS scale rates frequency and severity and has been used to ascertain the occurrence of NMS in a wide variety of PD cohorts, although largely in the white population.⁵²

A literature survey of NMS in Asian countries found that a high prevalence of NMS was noticed across all the ethnic groups.⁵³ Further evidence shows that between 90% and 100% of patients report at least one NMS, irrespective of their ethnic background, be it white, Asian, Middle Eastern or African.^{3,53-56}

Reports from another study involving the validation of the Chinese NMS scale revealed that the scale's total score was 31.06 ± 30.88 in Asians⁵⁷ versus 56.46 ± 40.66 previously reported in white people.⁵² However, these differences were also attributed to different basic demographic data, such as age, disease duration and motor stage (ie, Hoehn and Yahr stage⁵⁸).⁵⁷ Other studies in Asia (with similar mean age, mean disease duration and median Hoehn and Yahr stage) showed a much higher burden, which was 133.2 ± 47.5 .⁵⁹ In Tunisia, the validation study of the Arabic

version of the NMS scale reported a mean NMS scale total score of 82 ± 56 .⁶⁰ In conclusion, it appears that NMS burden assessed with the NMS scale is high across all ethnic groups. More detailed conclusions might only be drawn after further prospective comparative controlled studies.⁵³

Factors that may affect ethnic differences in Parkinson disease

Several factors have been described and explored in order to attempt explanations for the possible impact of ethnicity on PD. Branson and colleagues⁶¹ highlighted the wide range of influencing factors that have to be taken into account. In their recent review, they showed that there were reports of racial disparities in most aspects of PD, from knowledge of the disease to diagnosis and, finally, treatment.⁶¹

Firstly, variations between ethnic groups are evident when considering comorbidities — with a higher rate of diabetes among the Asian population⁶² — but further research is required to establish whether this difference in comorbidities influences the symptom expression of PD. In addition, dietary habits have been suggested to be different across ethnic groups and may also play a role.^{49,54,59,63} As an example, the Mediterranean diet has been associated with a decreased rate of manifest PD,^{14,64} while the frequent consumption of raw vegetables has been associated with an increased rate, according to a study in Hong Kong.⁶⁵ A recent review has summarised the possible connection between nutrition and neurodegeneration discussing possible underlying mechanisms, such as an inflammatory process.¹⁴

Moreover, cultural differences and beliefs might be influencing the observed differences among ethnic groups — several other medical conditions have addressed beliefs and significant differences have generally been reported.³⁴ For example, one study reported that African Americans and Chinese Americans perceived parkinsonian symptoms as a part of normal ageing, predisposing them to a delay in diagnosis and treatment and, thus, to poorer clinical outcomes.⁶⁶ A study in cognitive decline has shown that, in some cultures, cognitive decline might be regarded as something that should be kept private, which may also be applicable to PD and may influence the reporting and expression of symptoms in a clinical setting.⁶⁷

Further, race and ethnicity are concepts that are often applied in different contexts; these concepts changed over time and there exist large differences in culture and genes within one ethnic group.⁶⁷ Genetic differences across ethnic groups also need to be considered. It has been suggested that various genetic mutations play a role in observed differences across ethnic groups, including frequency and clinical presentation of PD,⁶⁸ and that the contribution of several genetic factors is different between ethnicities.⁶⁹ In spite of the prevalence of a genetic mutation, it might not necessarily translate into the same clinical expression across all ethnic groups,¹² which has to be further clarified in the context of PD. As an example, to date, different frequencies of variants of the *LRKK2* gene have been associated with the risk of developing PD in a varying population. The G2019S variant appears to be commonly found in North African Arab and Ashkenazi Jewish patients, while the G2385R and R1628P variants are found more commonly in selected Asian populations.⁷⁰ Varying carrier frequencies have also been described for *GBA* mutation.^{71,72} While the *GBA* N370S mutation is most commonly reported in Ashkenazi Jewish populations and has been rarely reported in the Asian population, the L444P mutations appear to be more frequent in

Factors that may explain variability of clinical phenotype and natural history observed in Parkinson disease across different ethnicities^{6,53,81}

- Life expectancy and length of survival with Parkinson disease
- Comorbidities
- Diet/nutritional status
- Cultural differences and beliefs
- Sociocultural habits
- Sociodemographic habits
- Perception of race/ethnicity concept
- Pharmacogenetics
- Other environmental issues
- Local guidelines, access and approach to (specialised) care and treatment
- Pharmacoeconomics and social factors (inequalities of health care)

Asians.⁷² In addition, the clinical expression of PD might vary depending on the underlying mutation.⁷³ For example, *LRRK2* G2019S or R1628P mutation carriers have been reported to present with increased lower extremity involvement at onset and postural instability and gait difficulty.⁷⁴ On the other hand, *GBA* mutations have been linked to an increased NMS burden, with higher degree of impaired cognitive function.⁷⁵ How and if these genetic mutations can be applied to ethnic differences is currently unknown.

Variations in the catechol-O-methyltransferase enzyme, which influences the rate of levodopa metabolism, have been described in the literature, with a possible increased prevalence of the variant that metabolises levodopa quicker among the African population compared with white people.⁷⁶ At least partly, this variation might be associated with the described differences in response to levodopa replacement therapy. In addition, environmental factors should also be considered. So far, aspects such as living in a rural area, well water use, exposure to pesticides and heavy metals have been reported to increase the risk of developing PD.⁶⁷

Finally, it has been suggested that access and approach to specialised treatment can vary considerably between different ethnicities,^{34,77} including differences in insurance coverage, quality of care, and inpatient behaviour, in particular, towards help seeking and compliance. A delay in diagnosis and treatment can have a dramatic negative impact on disease severity and disability.⁷⁸ In the United States, it has been shown that patients from minority backgrounds receive lower quality of care and have higher barriers to access treatment.⁷⁹ Several studies have reported a decreased number of referrals for deep brain stimulation in African Americans compared with their white counterparts.⁶¹

When investigating clinical symptoms and living with PD, such as acceptance of the condition and family support, pharmacoeconomics and social factors need to be considered. However, new studies dealing with this complex problem are lacking. The use of alternative medicine may also play a key role. It has been shown that, for instance, in India, most patients use traditional medicine, which might influence the presentation of their parkinsonian symptoms.⁸⁰ The Box summarises the possible factors that may explain the variability of clinical phenotype and natural history observed in PD across different ethnicities.⁴

Future implications

To date, the role of ethnicity in PD is poorly understood and is a very complex issue. Within these caveats, current literature proposes that ethnicity has at least partly an impact on clinical expression including motor and non-motor symptoms. In addition, there might be a link between ethnicity and pharmacogenomics, presenting as different responses to drug treatment, as exemplified with the varying activity of the catechol-O-methyltransferase enzyme. Further, there may be variability in genetic expression among different ethnic groups which may subsequently translate into clinical phenotypes (eg, *GBA*), since such ethnic differences might influence the pathophysiology of PD at least partly. However, what is currently available in the literature may not be truly representative. Moreover, it is difficult to compare currently available data because race and ethnicity have not always been defined consistently.^{12,82}

We live in a global world, but our understanding and the management strategy for PD are largely based on data on white people. We are now aware that, contrary to previous beliefs, PD is also common in non-white populations across the world. However, robust clinical studies dealing with epidemiology, natural history, clinical symptom expression and management in these populations are lacking.⁵ For example, the delivery of advanced therapies based on non-oral strategies in PD remains an unmet need.

In order to accurately investigate the incidence and prevalence of PD worldwide and establish if there are actual differences across ethnic groups, an inclusive and comprehensive global epidemiological study is warranted. Such study would allow the growing need for management of the second most common neurodegenerative disease to be truly dealt with,⁶¹ which is also important for the future development of public health services.¹² By further understanding the possible differences in PD across various ethnic groups, researchers and clinicians may gain new crucial insights into the underlying aetiologies, pathogenesis, expression and treatment response of PD.¹² Ethnic differences in pharmacogenetics, pharmacoeconomics and pharmacogenomics should be considered by health professionals and policy makers in relation to the holistic management of a patient with PD, which directly leads to the newly emerging concept of improved personalised medicine.⁸³

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