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Clinical non-motor phenotyping of Black and Asian Minority Ethnic compared to White individuals with Parkinson's disease living in the United Kingdom

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Abstract

Background: Ethnic phenotypic differences in Parkinson's disease (PD) are important to understand the heterogeneity of PD and develop biomarkers and clinical trials.

Objective: To investigate (i) whether there are non-motor symptoms (NMS)-and comorbidity-based phenotypic differences between Black, Asian and Minority Ethnic (BAME) and White PD patients and (ii) whether clinically available biomarkers may help differentiate and explain the diversity.

Methods: This is a multicentre (four sites, London), real-life, cross-sectional study including PD patients of BAME or White ethnicity. The primary outcome was a detailed NMS assessment, additional measurements included disease and motor stage, comorbidity, sociodemographic parameters and brain MRI imaging.

Results: 271 PD patients (54 Asian, 71 Black and 146 White) were included balanced for age, gender and disease severity (HY). Black patients had a shorter disease duration compared to White and Asian populations. The SCOPA-Motor activities of daily living scores as well as the NMSS scores were significantly higher in both Black (total score and domain "miscellaneous") and Asian (total score and domains "sleep/fatigue", mood/apathy" and perception/hallucinations) than White individuals. Both BAME populations had higher prevalence of arterial hypertension, and the Black population had a higher prevalence of diabetes mellitus. Brain MRI revealed a greater severity of white matter changes in Black compared to the White and Asian cohorts.

Conclusion: These findings suggest differences in phenotype of PD in BAME populations with greater burden of NMS and motor disability and a higher rate of cardiovascular comorbidities.

Introduction

Parkinson's disease (PD) is now widely considered as a heterogeneous syndromic condition comprising both motor and non-motor features [1-3]. Identifying clinically relevant subtypes is important to advance our understanding, stratify for clinical trials and improve management by true delivery of personalised treatment[4]. Ethnic differences in clinical features have been reported in Alzheimer disease, Stroke, Multiple sclerosis, and cardiovascular disease with higher rates of stroke, diabetes and hypertension in Black, Asian and minority ethnic (BAME) populations [5-9]. Furthermore, epidemiologic evidence suggest that ethnicity has an important impact on genetic, epigenetic, environmental, cultural and socioeconomic factors, which in turn may affect the pathophysiology and symptom expression in PD [5, 8, 10, 11]. PD numbers worldwide are projected to double by 2030 and India for instance are estimated to have the highest number of PD patients along with China by that time[12]. Phenotypic differences, if present between White and BAME subjects, are therefore relevant particularly as a greater disease burden has been reported in BAME[11, 13, 14]. The specific differential characteristics of motor and non-motor symptoms (NMS) in BAME PD patients have never been addressed in a systematic approach using validated tools. Given its multi-ethnic population, the London area allows to study and compare different phenotypes in multi-ethnic populations. This study builds on an existing database of BAME PD patients at King's College Hospital since the early 2000's with data reported previously[11].

The main objective was to analyse the NMS clinical profiles of the main BAME groups living in the London area, namely Asian and Black compared to White patients, using the NMS scale (NMSS)[15] and other motor and non-motor tools.

Methods

Study design

This was a cross-sectional analysis from a multicentre, prospective, observational real-life study (UK National Institute for Health Research clinical research network (UKCRN) number:18278) called "Nonmotor symptoms of Parkinson's in a multi-ethnic population", as part of the Non-motor Longitudinal International cohort study (NILS;UKCRN number:10084). The study was carried out in accordance with the Declaration of Helsinki and authorised by the local ethics committees. All patients gave written consent prior to participating in the study between 27th of January 2015 and 1st of April 2018. All data were stored at the National Parkinson's Centre of Excellence, King's College Hospital in compliance with the National Data Protection Act (United Kingdom (UK) Reg: Z6614305) and compliant with General Data Protection Regulation (GDPR) (EU) 2016/679.

Patients

PD patients based on UK Brain Bank criteria and self-reported ethnicity (Asian, Black, or White) attending clinics across London [16-18].

Assessments

Age, gender, disease duration were noted and levodopa equivalent daily dose (LEDD) calculated[19]. Ethnicity was assigned as per Office for National Statistics from the Census 2011 in England and Wales[16]. The terminology of ethnicity is different across countries; however, as this is a UK based study we have elected to align with the official standardised Census criteria. Birth and age when moved to the UK, educational level, civil status, employment activity, potential environmental risk factors, body mass index, cardiovascular and metabolic risk factors were recorded[20].

The following assessments were performed:

Nonmotor assessment

- NMSS, a health-professional completed tool including 30 items grouped in nine domains, the NMS burden was graded as 0=none, 1-20=mild, 21-40=moderate, 41-70=severe, >70=very severe (total score)[21]
- NMSQuestionnaire, which was used to assess non-declaration of NMS[22]
- Hospital Anxiety and Depression scale (HADS)[23]
- Minimental State Examination (MMSE)[24]
- Parkinson's Disease Sleep Scale (PDSS)[25]
- Epworth Sleepiness Scale (ESS)[26]

Motor assessment

- Hoehn and Yahr (HY) stage[27]
- Scales for Outcomes in Parkinson's Disease-Motor scale (SCOPA-Motor scale)[28, 29]

Neuroimaging (in a subsample of 63 patients)

- Magnetic resonance imaging (MRI) on a 1.5 Tesla General Electric (GE) Signa HDx MRI system (GE Healthcare, Waukesha, WI, USA) or a 1.5 Tesla Siemens Avanto MRI system (Siemens, Erlangen, Germany). White matter changes (WMC) were assessed using the age-related white matter changes (ARWMC) scale, rating the severity of white matter changes [30]. The total scores (sum of white matter and basal ganglia lesions) were analysed. The scores range from zero (no lesions) to 6 (maximum severity). Microbleeds were assessed using T2*-weighted gradient-recalled echo (GRE) imaging and susceptibility-weighted imaging (SWI) if available on cerebral MRI images [31]. Ventricular enlargement was measured by the Evan's Index (ratio of the maximal width of frontal horns to largest diameter of the inner

skull in the same slice)[32] with a pathological cut-off value of 0.3 (EI ≥ 0.3)[32]. All the scoring was performed by the same neuroradiologist blinded to ethnicity and name.

Statistical analysis

Normality of distribution was assessed visually by using frequency distribution histograms. Differences between the three ethnic groups were analysed with Kruskal–Wallis tests or 1-way ANOVA analysis of variance if parametric tests were applicable. Post-hoc analysis between pairs of groups were made when the initial test across all groups was statistically significant. Comparison between pairs was performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. For comparisons between two ethnic groups the independent-samples t-test or Mann-Whitney U test respectively was used.

To investigate if there were statistical differences in categorical variables between the three different ethnic groups, Pearson's chi-square or Fisher's exact test was applied.

All analyses were conducted using Statistical Package for Social Science (version 23.0 for Mac; SPSS). A p-value <0.05 was considered to be statistically significant.

Results

Basic characteristics

Out of 316 patients 45 subjects were excluded (7 patients were diagnosed with atypical Parkinsonian disorder at follow up, 17 patients reported to have mixed ethnic background and 21 had not completed the main outcome tools). Out of 271 patients included, 54 were Asian, 71 Black, and 146 White. Baseline values are summarised in Table 1. The majority of Asian patients were first generation immigrants born in South Asia and India (31.5%), followed by Sri Lanka (14.8%) and Kenya (11.1%) who had moved at an average age of 27.9 years (±13.2) to the UK. Most White PD patients were born in the UK (95.2%). The majority of

Black patients were born in Jamaica (38.6%) or Nigeria (21.4%), and had immigrated to the UK at an average age of 26.7 years (±13.6).

The majority of White and Black patients completed high school as the highest degree (50% and 48.6%) while the majority of Asians completed university as highest degree (55.6%) ($p<0.001$). There were also significant differences in civil status with 21.1% of Black patients reported to be separated/divorced compared to 7% in the White and Asian population ($p<0.05$). There were no significant differences in employment status between the three ethnic groups; among all groups, the majority of patients were retired.

The Black population had a significant shorter disease duration compared to the White population and shorter disease duration and lower LEDD compared to the Asian population.

Motor assessment

The SCOPA-Motor Activities of Daily Living (ADL) score was significant higher in the Asian and Black compared to the White group, SCOPA-Motor scale total score was higher in the Asian compared to the White individual group with a trend towards a higher score in the Black compared to the White group (Table 2).

Burden (severity and frequency) of non-motor symptoms (Non-Motor Symptoms Scale)

The NMSS Total scores were significant higher in the Black and Asian (severe burden) than the White (moderate burden) PD sample (Table 3)[21]. There were no statistically significant differences in NMSS total score and domains between the Asian and Black PD populations. Asian patients had higher scores on the domains “sleep/fatigue”, mood/apathy” and “perception/hallucinations” than White patients (Table 3).

- Significantly worse NMS items were “fatigue” (4.4±3.0 versus 2.5±3.0, p=0.002), “losing interest in surrounding” (2.7±4.1 versus 1.1±1.9, p=0.023), “being nervous, worried or frightened for no apparent reason” (3.6±2.7 versus 2.4±1.4, p=0.016), “being sad or depressed” (3.0±3.8 versus 1.4±2.3, p=0.002) and “difficulties

experiences pleasure from usual activities" (1.7±2.9 versus 1.6±0.6, p=0.025). No significant differences between the items of perception domain.

Individuals in the Black cohort had significantly higher scores in the NMSS domain "miscellaneous" compared to the white group.

- Significantly worse NMS items included "pain" (2.8±3.8 versus 1.6±2.7, p = 0.014), and "unexplained change in weight" (1.1±2.3 versus 0.5±1.7, p = 0.002)

Other non-motor measurements

The Black cohort had significantly lower MMSE scores compared to the White cohort but there was no difference on HADS, PDSSS and ESS (Table 3). The Asian group had significantly more impairment on the HADS ($p<0.001$), with significant higher impairment in the depression domain (($p<0.001$) and a trend to significant difference in the anxiety domain ($p=0.052$) and PDSS ($p = 0.008$) compared to the White group.

Non-declaration of nonmotor symptoms according to the NMSQuest

The frequency of non-declaration of NMS was 38.6% for Black, followed by 37.0% within the Asian and lowest with 29.2 % in the White population ($p=0.381$).

Comorbidities

Both the Asian and Black populations reported higher prevalence of arterial hypertension compared to the White population, and the Black population had a significantly higher prevalence of diabetes mellitus (type 1 and type 2) than the White population. BMI and the prevalence of hyperlipidemia were similar across all groups. The prevalence of smoking was similar across all groups, while the White population reported consuming significantly more alcohol than the Black and Asian populations.

Reported exposure to insecticides and pesticides (Asian 20.8%, Black 20.3% and White 22.3%, $p = 0.937$) was not significantly different across the three ethnic groups (table 1).

Imaging

In total 63 patients with a cerebral axial Proton density/T2 spin echo MRI scan were considered for this analysis. Among those, 30 (46.8%) were White, 14 (22.6%) Asian and 19 (30.2%) Black. On average, the white matter changes in White and Asian PD patients were rated as insignificant while Black patients had on average mild white matter changes. There was no evidence of very severe white matter and basal ganglia lesions in any patients and only 4 patients had basal ganglia changes. The severity of white matter changes was

significantly higher in the Black compared to the White and Asian cohort (Mean ARWMC total score 1.2±1.0 versus 0.5±0.8 versus 0.4±0.5 respectively, p =0.012). There were no significant differences between the White and Asian cohort. Cerebral microbleeds and mean Evan's Index were similar across the groups (p=0.254).

Discussion

To our knowledge, this is the first systematic study based on a well characterised BAME and White multi-ethnic PD cohort comparing and contrasting the demographic, clinical and biomarker profiles with a specific focus on NMS. Our data support the notion that BAME patients experience a higher NMS burden and comorbidity compared to the White PD cohort, with slightly different phenotypes within the Asian and Black PD communities[11, 33]. The pathophysiological basis of these phenotypic variability observed between different ethnic cohorts remains unclear but the significant differences in cardiovascular risk factors may play an important role.

The Asian group

We confirmed previous observations that Asian patients have worse motor disability scores that White patients after similar disease duration [11]. Asian patients also had a higher non-motor burden with higher rates of fatigue, sleep dysfunction, anxiety and depression. Fatigue is a common NMS of PD and a fatigue-dominant serotonergic subtype of PD overlapping with somnolence has been proposed [34-39]. The higher prevalence of depression in the Asian population should alert health-care professionals to this group's increased risk of these neuropsychiatric complications [40].

The Black group

The characteristic features seen in the Black PD population were the higher degree of both motor disability and non-motor impairment. They also had a significantly shorter disease duration than in the White population. A more rapid progression in this population has been previously postulated in the South London population[10, 11] but no prospective data is currently available. It is also possible that Black patients are diagnosed later which is

supported by the similar Hoehn and Yahr stage, lower LEDD and higher rate of non-declaration of NMS. In a US-based study African-Americans were reported to have been less likely to be diagnosed with PD and when diagnosed, were diagnosed at a later stage of disease [41]. It is notable in this context that almost 40% of the Black PD did not have their nonmotor symptoms recognised and this issue is an important pointer towards refining delivery of health care for black and minority ethnic patients. As recently outlined by Hurt et al., there are several explanations for non-declaration and non-recognition, including culturally factors[42]. We did not address the cause in detail and future studies should address these in a multi-ethnic, multi-cultural PD population.

Black population also reported significantly worse NMSS burden particularly in the items pain and change in weight. Ethnic disparities in relation to pain in the general population have been reported with a general trend that Africans report greater pain and suffering compared to Whites across different conditions and environments[43]. Several causes have been suggested ranging from varying pain thresholds, genetic variability, sociocultural differences, Vitamin D levels and sleep quality[43, 44]. However, in our study we did not specifically address these issues. It is also unclear why Black patients reported greater rates of changes in weight than White patients. This may be related to the higher comorbidity of diabetes mellitus, but we do not know the direction of weight change and comparisons to non-PD populations.

We also found they had greater cognitive impairment as assessed on the MMSE than White patients with PD, a finding that has been reported before [11, 45, 46]. However, the fact many Black participants did not have English as their first language and limitations in the use of the MMSE in patients with different educational levels need to be considered in the interpretation of this result. The MMSE was used as this was the preferred option when the NILS study started in 2011. Notwithstanding, this finding might serve to signpost a higher

risk of cognitive deterioration in the Black PD group[47]. Whether this suggest a higher rate of the cholinergic cognitive subtype of PD remains to be confirmed[1, 48, 49].

Biomarkers and other contributing factors in relation to ethnic phenotypes

A higher load of white matter changes in the Black compared to the White and Asian cohort was found. Differences between ethnic groups in the presence of white matter changes have been reported although there is controversy in the literature[50, 51]. White matter changes in PD might be partly linked to certain NMS including cognitive impairment, orthostatic hypotension as well as gait disorders[52-54]. In addition, diabetes and arterial hypertension are also associated with an increased risk of white matter changes. We speculate that the increased white matter changes in our Black PD cohort is therefore likely to be associated with comorbid vascular disorders[11, 55]. Exposure to environmental factors such as insecticides and pesticides has been postulated to be one of the risk factors to develop PD[56]. In our cohort, no significant differences in exposure to insecticides and pesticides were reported, making it unlikely that the observed clinical differences are related to this environmental factor.

Another important aspect that might to drive ethnic differences are social factors such as educational levels and civil status; a study on freezing of gait (FOG) for instance has reported that patients with lower education were more likely to suffer from FOG[57]. In our cohort, the Asian population had higher educational levels and also had higher NMSS burden levels compared to the Black population. The differences in educational level are therefore unlikely to explain the observed differences in NMS although access to education and information about PD was not specifically addressed. Furthermore, significant differences in civil status were found (20.8% of Black patients reported to be separated/divorced compared to 7% in

the White and Asian population). To date, there is no literature on the potential influence of civil status on the observed ethnic differences.

There are several limitations to this study. To our knowledge, this is the first real-life cohort study in a multi-ethnic population living in the UK. As such we were interested to characterise the population presenting in clinic and participant characteristics were reflective of the clinic population and were not matched for disease duration or severity. The study was also cross-sectional and we were therefore not able to study disease progression prospectively. We also cannot exclude a selection bias in recruitment, although we used unselected NHS clinics to identify and approach participants.

The current study however has demonstrated the feasibility of a study to examine phenotypic differences in a multi-ethnic PD population across London. The findings emphasise differences in phenotype of PD in the BAME population with greater burden of NMS and motor disability and a higher degree of cardiovascular comorbidity. The findings raise important scientific, social and clinical issues to address the challenges of care delivery in a "hard to reach population" in health services that serve a diverse multi ethnic population. The results of the study could lead to further work that could drive the development of specific personalised care packages for different ethnic groups, similar to a recent study in pain showing that tailoring care to the needs to specific ethnic groups using a language specific and culturally adopted pain management programme helped to break down cultural barriers but also increase awareness of the cultural perception and experience of persistent pain [58]. Further studies are now needed to confirm the observed differences and assess the precise causes and contributing factors. Furthermore, future studies need to take into account the significant diversity among the overall Asian and Black populations, which was not possible to take into consideration in the present study. Finally, these findings set the scene

for a large-scale multicentre cohort study with a focus on specific biomarkers and ethnicity which are currently an unmet need.

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Competing interests

The authors declare that they have no conflicts of interest.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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Table 1 – Baseline values by ethnicity

	Asian (N =54)	Black (N=71)	White (N = 146)	p-value	p-adjusted		
	Mean (SD)	Mean (SD)	Mean (SD)		Asian vs White	Black vs White	Asian vs Black
Basic characteristics							
Age (years)	66.4 (11.4)	67.2 (11.7)	67.2 (12.7)	0.908 [Y]			
Gender, male (%)	66.7	62	58.9	0.609[Z]			
Disease duration (years)	7.2 (6.2)	3.6 (3.4)	5.7 (5.2)	**<0.001** [X]	0.22	**0.009**	**<0.001**
Age at PD onset (years)	59.2 (13.2)	63.6 (12)	61.4 (13.5)	0.165[Y]			
Hoehn and Yahr (Median, IQR)	2 (2-3)	2 (2-3)	2 (2-3)	0.376 [X]			
LEDD TOTAL (mg)	675.5 (517.2)	455.4 (393.8)	606.9 (552.6)	**0.025** [X]	0.491	0.21	**0.022**
LEDD (Dopamine agonists only)	148.88 (189.11)	89.65 (46.55)	148.77 (178.07)	**0.001**[x]	0.951	**0.001**	**0.001**
Cardiovascular risk factors							
BMI (kg/m^2)	26.4 (4.6)	27.8 (6.4)	26.5 (5.5)	0.289 [Y]			
Hyperlipidemia (%)	33.3	31.4	24.8	0.380 [Z]			
Arterial hypertension (%)	46.3	52.9	27.6	**<0.001** [Z]	**< 0.05**	**< 0.05**	> 0.05
Diabetes mellitus (%)	24.1	28.6	13.1	**0.026** [Z]	> 0.05	**< 0.05**	> 0.05
Currently smoking cigarettes (%)	6	3	4.2	**0.411**			
Units of alcohol per week	1.1 (3.6)	0.9 (2)	5.4 (9.3)	**<0.001**	**<0.001**	**<0.001**	1

Abbreviations: N = Number, BMI = Body mass index; LEDD = Levodopa equivalent daily dose; PD = Parkinson's disease; SD = Standard deviation; vs = versus; IQR = Interquartile Range

[X]Kruskal-Wallis rank test was used to test differences between the three ethnic groups. Post hoc analysis was performed between the pairs of ethnicity when statistically significant; multiple comparisons were corrected with Bonferroni method.

[y]One-way Anova was applied to test differences between the three ethnic groups.

[z]Pearson Chi-square test was used to test differences between the three different ethnic groups. Post hoc analysis was conducted between the pairs of ethnicity.

In bold highlighted all significant results

Table 2 - Characteristics of motor impairment by ethnicity

	Asian (N =54)	Black (N=71)	White (N = 146)	p-value	p-adjusted		
	Mean (SD)	Mean (SD)	Mean (SD)		Asian vs White	Black vs White	Asian vs Black
SCOPA-Motor Scale Total	21.0 (11.4)	19.5 (8.5)	16.5 (9.1)	**0.004** [Y]	**0.008**	0.081	1.000
SCOPA-Motor Scale – Motor impairment	11.4 (6.3)	11.7 (5.1)	10.3 (5.5)	0.146 [X]			
SCOPA-Motor Scale - ADL	7.6 (5.1)	6.6 (3.8)	4.9 (3.4)	**<0.001** [X]	**0.002**	**0.015**	1.000
SCOPA-Motor Scale - Complications	2.0 (2.7)	1.2 (1.8)	1.2 (2.2)	0.094 [X]			

Abbreviations: N = Number; SCOPA = Scales for outcomes in Parkinson's disease; SD = Standard deviation; ADL = Activities of Daily living; vs = versus

[X] Kruskal-Wallis rank test was used to test differences between the three ethnic groups. Post hoc analysis was performed between the pairs of ethnicity; multiple comparisons were corrected with Bonferroni method.

[y] One-way Anova was applied to test differences between the three ethnic groups. Post hoc analysis was performed between the pairs of ethnicity; multiple comparisons were corrected with Bonferroni method.

In bold highlighted all significant results

Table 3 – Domain based data from non-motor symptoms scale and other non-motor measurements (sleep, anxiety, depression, cognition) by ethnicity

	Asian (N =54)	Black (N=71)	White (N = 146)	p-value	p-adjusted		
	Mean (SD)	Mean (SD)	Mean (SD)		Asian vs White	Black vs White	Asian vs Black
Non-motor symptoms scale (Domains and total score)							
Cardiovascular	1.7 (2.6)	2.2 (3.3)	1.6 (2.8)	0.372			
Sleep/fatigue	12.7 (11.4)	9.7 (9.4)	7.3 (7)	**0.014**	**0.013**	0.505	0.467
Mood/ Apathy	13.8 (16.5)	10.6 (13.6)	6.4 (10)	**0.009**	**0.010**	0.271	0.657
Perception/ Hallucinations	2.1 (4.2)	1.5 (3.3)	1.2 (3)	**0.049**	**0.046**	0.832	0.618
Attention/ memory	6.7 (9.2)	5.1 (6.4)	4.7 (5.9)	0.658			
Gastrointestinal	5.4 (6.9)	3.5 (4.4)	3.4 (4.7)	0.246			
Urinary	10.2 (11.3)	9.4 (10.0)	5.8 (7.4)	**0.033**	0.192	0.062	1.000
Sexual function	2.4 (5.8)	2.1 (4.6)	0.9 (2.8)	0.069			
Miscellaneous	7 (9.3)	7.6 (6.3)	5.4 (6.3)	**0.025**	1.000	**0.021**	0.232
NMSS Total	62 (52.8)	51.2 (40.3)	36.4 (29.5)	**0.004**	**0.016**	**0.033**	1.000
Other non-motor assessments							
MMSE Total	28.1 (2.4)	26.9 (3.3)	28.4 (2.7)	< **0.001**	0.375	< **0.001**	0.220
CISI-PD Total	8.4 (3.9)	7.5 (3.4)	6.8 (3.6)	0.052			
HADS Total	15.2 (8.2)	11.6 (6.8)	10.6 (7.1)	**0.001**	**0.001**	0.839	0.055
PDSS Total	92.8 (34)	101.6 (29.1)	109.3 (21.8)	**0.008**	**0.008**	0.253	0.632
ESS Total	8.2 (6.1)	7.6 (5.6)	7.1 (5.2)	0.594			

Abbreviations: N = Number; SD = Standard deviation; NMSS = non-motor symptoms scale; MMSE = Mini-Mental State Examination; Clinical Impression and Severity Index; HADS = Hospital and Anxiety Scale; PDSS = Parkinson's Disease Sleep Scale; ESS = Epworth Sleepiness Scale; vs = versus

-Kruskal-Wallis rank test was used to test differences between the three ethnic groups. Post hoc analysis was performed between the pairs of ethnicity; multiple comparisons were corrected with Bonferroni method.

In bold highlighted all significant results

Appendix 1. Authors.

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