THE PROFILE OF PATIENTS WITH IDIOPATHIC PARKINSON'S DISEASE IN A SOUTH AFRICAN HOSPITAL COMPLEX-

AN INSTITUTION BASED OBSERVATIONAL STUDY.

A RESEARCH ARTICLE SUBMITTED TO THE UNIVERSITY OF THE WITWATERSRAND FOR THE PURPOSE OF THE DEGREE OF MASTER OF MEDICINE, NEUROLOGY.

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Final submission

Declaration

I, Marcelle Smith, declare that this research report is my own work. I am submitting it to the University of the Witwatersrand. It has not been previously submitted for any degree or other purpose at this or any other university.

Signature: 

Date: 28 March 2017

University of the Witwatersrand, Johannesburg

School of Clinical Medicine

SENATE PLAGIARISM POLICY

Declaration by Students

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I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

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I have followed the required conventions in referencing the thoughts and ideas of others.

I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this in not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature: _____
Date:_28/03/17_____

THE CLINICAL PROFILE OF IDIOPATHIC PARKINSON'S DISEASE IN A SOUTH AFRICAN HOSPITAL COMPLEX - THE INFLUENCE OF ETHNICITY AND GENDER

Marcelle Smith and Girish Modi

Abstract:

Idiopathic Parkinsons Disease (IPD) has not been well studied in Black African populations. Data on the demographics, phenotype differences with Caucasoid populations, severity and frequencies of IPD in Black Africans is scant.

Aim: to determine the impact of ethnicity and gender on the phenotype of IPD in South African patients.

Method: Fifty patients with diagnosed IPD were recruited. The data collection was in the form of a questionnaire and clinical evaluation which included a mental status examination (MMSE), and illness staging.

Results: Thirty-five patients were Black African, eleven were white European descendant, three were of Indian descent and one had mixed ancestry. Twenty-eight of the patients were female. There were no significant gender differences within or between the different ethnic groups. Seventy- one percent of black and ninety-one percent of white participants had classic IPD presentations. A resting tremor was found in fifty-nine percent of all males in the study but in ninety-four percent of females. In the black IPD patients, thirty-one percent had

early onset IPD (age of onset less than 50 years) with a gender ratio of M:F=1:6. Twenty-nine percent had an akinetic-rigid syndrome with erect posture and no tremor (gender ratio of M:F = 7:4) and seventy-four had cognitive impairment (gender ratio of M:F =8:5).

Conclusion: The phenotype of IPD in the majority of our study population is of the classic IPD type. In a third of our Black patients the onset was early and in a third the presentation was akinetic.

Keywords: Parkinsons disease; Gender; Ethnicity

Acknowledgements

I would like to thank the Division of Neurology for all the support during this process, and to all those who participated in the study.

CONTENTS

1. RESEARCH PROTOCOL WITH EXPANDED LITERATURE REVIEW

The profile of patients with Parkinson's disease in a South African hospital complex- an institution based observational study.

Introduction and literature review

Idiopathic Parkinson's disease (IPD) was first described by James Parkinson in 1817[1] and later his work was continued by Gowers and Charcot. It is a slowly progressive, degenerative neurological disorder characterised by the syndrome of parkinsonism . This encompasses the cardinal features of bradykinesia, muscle rigidity, resting tremor, stooped posture and loss of postural reflexes with falls and freezing. There is little literature on IPD from South Africa, and Africa as a whole. Most available information is derived from European and North American populations.

The diagnosis of IPD is made on clinical grounds. In 1988, Gibb and Lees developed the Queen Square Brain Bank (QSBB) criteria for PD, based on correlation of clinical features of IPD with pathological confirmation from post mortem examination of the brain[2]. In 1992, Hughes et al showed that only 76% of patients diagnosed IPD by UK neurologists had the neuropathological features diagnostic of the disease[3]. Retrospective application of the QSBB clinical criteria improved the diagnostic accuracy to 82%. The study was revisited in 2001 and showed that the clinical diagnosis accuracy had improved to 90%[4]. The QSBB criteria are highly sensitive and specific and so remain the benchmark for the diagnosis of IPD. Strict adherence to the criteria enables a reliable diagnosis. It is, however, important to note that not all patients will meet the full diagnostic criteria for IPD at initial presentation.

The Queen's Square Brain Bank (QSBB) criteria, entail a three step process. In the first step, a diagnosis of a syndrome of parkinsonism must be made.

The hallmark of parkinsonism and essential criterion is the presence of bradykinesia. Additionally, the patient must have one of the following clinical features

- muscle rigidity, resting tremor (4-6Hz),
- postural instability that is not related to visual, cerebellar, vestibular or proprioceptive dysfunction.

The second step is to apply exclusion criteria. These are chiefly derived from the patient's history. These include the following:

- Repeated strokes with stepwise progression

- Repeated head injury
- Antipsychotics or Dopamine-depleting drugs
- Definite encephalitis and/or oculogyric crisis on no drug treatment
- More than one affected relative
- Sustained remission
- Negative response to large doses of levodopa (if malabsorption excluded)
- Strictly unilateral features after 3 years
- Other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski's sign, early severe dementia with disturbance of language, memory or praxis
- Exposure to known neurotoxin
- Presence of cerebral tumour or communicating hydrocephalus on neuroimaging

The third step is to look for supportive criteria for IPD.

The third step includes features that are supportive of IPD. Three or more of the following criteria are required:

- Unilateral onset
- Resting tremor present
- Progressive disorder
- Persistent asymmetry affecting the side of onset most
- Excellent response to levodopa (70-100%)
- Severe levodopa-induced chorea
- Levodopa response for more than 5 years
- Clinical course of over 10 years

With advances in genetic research, many forms of Idiopathic Parkinson's Disease have been found to result from genetic mutations in genes encoding alpha synuclein and the Parkin protein, among others. Up to 50% of patients with early onset IPD have the Parkin gene mutation. However, most cases are sporadic and of unknown aetiology. The disease arises from loss of neuromelanin-containing monoamine neurons, particularly dopaminergic neurons in the substantia nigra pars compacta.

Van Eeden et al carried out a study to determine the incidence of IPD by age, ethnicity and gender[5]. This was the first study of its kind. Newly diagnosed patients between 1994 and 1995 from an large health maintenance organisation in Northern California, the Kaiser Permanente Medical Care Program, were included in the study. A total of 588 newly diagnosed IPD patients were identified from the membership information. These patients were diagnosed according to the modified Core Assessment Program for Intracerebral Transplantation/ Hughes criteria. There was an overall incidence rate of 13.4 per 100,000. This increased greatly over the age of sixty. The mean age at diagnosis was 70.5 (38-91) for both men and women. White patients were found to be older at diagnosis compared to Black, Hispanic and Asian participants. The annual incidence of Parkinson's disease was 12.3% in people under 50 years old and 44% in those over 50. Only 4% of cases overall had onset of disease before the age of 50. The rate of PD was 91% higher in men than in women.

Wright Willis et al published an epidemiological study in 2010 which investigated the geographic and ethnic variation in PD[6]. The study population included patients who were Medicare users living in the USA in 1995 or between 2000 and 2005. Incidence and prevalence rates were determined by comparing the number of PD patients with the total number of Medicare users. The mean prevalence in users over the age of 65 years was 1.6% and the mean annual incidence of 1.85%. The mean prevalence slowly increased with age. The prevalence in Black and Asian users was 50% lower than in whites. It was also higher in urban areas than in rural areas. Black users also appeared to have a higher morbidity related to PD than White users. The question remains whether these results can be extrapolated to South African patients with PD, and whether PD found in our Black population is distinct from that found in white patients.

Although some of the earliest reports of Parkinson's -like disorders can be traced back as early as 1350-1200 BC Egypt, little is known about Idiopathic Parkinson's Disease in African populations. Most of what we know of the disease is derived from European and American studies.

A systematic review was conducted in 2006 by a group in Nigeria[7]. It featured articles that were published between 1944 and 2004. These studies emanated from 13 African countries, including South Africa. The review showed that incidence and prevalence rates of IPD appeared lower in Africa than those in Europe and North America. There were few genetic studies done in Africa, and none in blacks.

In 2010, the same group published a study that investigated the clinical profile of Parkinson's Disease in a population of patients in Lagos, Nigeria[8]. These results were extracted from a data base collected

over 10 years. Of the 124 patients with parkinsonism, 98 (79%) had Idiopathic Parkinson's Disease, while 26 (21%) had secondary PD. Results showed a similar disease profile to European counterparts, although there were fewer patients with early onset disease (<50 years old) and family history. Only 1,02% of all patients had a family history of PD. The frequency of young onset PD was 16.3%. In terms of clinical presentation, 31.6% were tremor- predominant, 55.1% were mixed, and 14.3% had an akinetic-rigid presentation. These different clinical presentations were not compared for gender. An important observation was that, compared to European studies, there was a greater delay in diagnosis. One of the negative aspects of this study was that patients with secondary Parkinson's disease were not excluded from the study.

Of the few studies that have come out of Africa, most have been prevalence studies. J.E. Cosnett published an observational study in 1988[9] which included 2638 patients from 3 major centres in Durban, South Africa. This was the first of its kind in South Africa. The prevalence of IPD was determined by calculating the frequency of levodopa usage. The results showed a lower prevalence of IPD in Black patients compared to White patients.

Van Der Merwe, et al. looked at the factors influencing the development of early onset (EOPD) or late onset Parkinson's Disease (LOPD)[10]. This data was extracted from a 5 year genetic study in Tygerberg Hospital in the Western Cape, South Africa. The study found that there is a high frequency of PD with early onset and positive family history in South Africa. EOPD was also found more frequently in Black, mixed-ancestry and White Afrikaner participants compare to White English speaking patients. This conflicts with the Lagos study's findings. A family history was associated with younger onset. However, one third of cases with LOPD had a significant family history. This challenges the assumption that LOPD is sporadic. Gender was found to have no effect on Age of onset. This was in keeping with other recent literature. Among participants, there was a male predominance. There were 62.5% more males with PD than females. Coffee and cigarette smoking had no impact. There were no definitive findings regarding environmental factors.

In terms of environmental risk factors, some metals and pesticides have been linked to the development of PD in people with chronic occupational exposure. The Farming and Movement Evaluation Study (FAME)[11], examined the relationship between PD and exposure to pesticides. This was a case-control study based in the United States with participants recruited between 1993 and 1997 from people with occupational exposure to pesticides and their spouses. A link was found between rotenone and paraquat and PD. This has been explained by mitochondrial dysfunction, oxidative stress, and the ubiquitin-proteosome pathway dysfunction. In 2000, Betarbet et al published experimental findings in rats that showed the presence of ubiquitin and alpha synuclein

containing cytoplasmic inclusions[12]. This was in response to rotenone treatment. Rotenone is commonly found in pesticides.

Haaxma, C et al. Published a study in 2007[13], to investigate gender differences in disease characteristics. Motor deterioration and nigrostriatal degeneration in Idiopathic Parkinson's Disease. The study sample included 253 participants with Parkinson's Disease who had not received treatment with either dopamine agonists or levodopa. Age of onset, presenting symptoms, severity and progression of motor features, and the amount and progression of nigrostriatal degeneration were all assessed. These factors were then compared to determine the influence of gender and oestrogen status. The results revealed that women had a slightly older mean age of onset (2.1 years). This may have been related to higher physiological striatal dopamine levels, possibly related to the influence of oestrogen. Women had and a higher prevalence of tremor and a milder deterioration, suggesting a more benign disease course.

Mayeux, R et al. carried out a population-based study to determine the prevalence of idiopathic Parkinson's Disease, in Washington Heights in New York[14]. The study was conducted from January 1988 to December 1993. A registry of patients with IPD was created by advertising on radio and television. Patients with and without dementia were included in the study. The prevalence of IPD in 99.4 per 100 000. This increased from 2.3 per 100 000 for patients younger than 50 years old, to 787.1 per 100 000 in those older than 80 years old. The study concluded that Idiopathic Parkinson's Disease was a frequent disease of the elderly. It affected men more than women, and White people more than non-white people.

In October 2005, Baba et al, published the results of a large clinic-based cohort study which determined whether there were gender differences in the phenotype of Idiopathic Parkinson's Disease[15]. Demographic, historical and clinical features were examined for differences between the two gender groups. A total of 1264 of individuals with IPD were assessed. The study sample was made up predominantly males (67%). There were no significant differences between the two groups, in terms of demographics and patient history. The frequency of a family history was also the same. The females in the sample did show a more advanced disease, as determined by the Hoen & Yahr staging. Females also had more severe dyskinesias as a result of Levodopa treatment. In terms of non-motor symptoms of IPD, a history of depression was much higher in females, compared to males (35% vs. 24%). This study did more to highlight more the similarities between the two gender groups, than differences.

In 2012 in Sardinia, Solla, et al. investigated whether gender played a significant role in the development and progression of Parkinson's disease[16]. 156 outpatients with Parkinson's disease were recruited into the study. 91 were male and 65 were female. The two groups were assessed for differences in motor and non-motor symptoms of IPD. The results showed that, in terms of motor

symptoms, females were more likely to present with tremor as the first symptom, compared to males. There were many differences between the two groups in terms of non-motor symptoms. With regards to autonomic dysfunction, the severity of cardiovascular involvement was worse in females, whereas sexual dysfunction was more frequent in males. Abnormal mood, usually depression, and anxiety were more common in females, however males showed more impulsive behaviour. This study highlighted the role that gender plays in the presence of motor and non-motor aspects of Idiopathic Parkinson's disease.

So far, studies of Parkinson's Disease in African populations have shown a lower incidence and prevalence compared to European and North American populations. The findings regarding the frequency of Early onset PD in Black patients has been inconsistent. A family history of PD is associated more frequently with a younger onset, but is found in a significant percentage of LOPD as well. There is also a greater delay in diagnosis of PD in Africa.

7) Objective

The purpose of this study is to describe the population of patients with Idiopathic Parkinson's Disease who attend the Neurology clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Hospital (CHBH). The description will include demographic information as well as clinical features, comorbidities, and treatment response. This will then be compared to the well documented European and North American populations in terms of age of onset, gender predominance, family history, most prominent clinical features etc. This is to determine whether IPD in our group of patients differs in any way to the well described Northern Hemisphere PD populations. Furthermore, the study is aimed at determining whether ethnicity and gender have any impact on the clinical presentation of IPD. There is anecdotal evidence that black patients may present with a distinctive clinical phenotype. The study will determine whether this is the case in our population of patients.

8) Method

(i) Study design and study population: This is an observational study using a questionnaire as well as cognitive testing by means of the Mini Mental State examination, grading of motor function with the Hoen and Yarh score, and grading of physical disability. The study will run from when final ethics approval is received, until 50 participants who meet the inclusion criteria are recruited. The questionnaire will be administered to both new and old patients with Parkinson's Disease who attend the Movement disorder/Parkinson's

clinic every Friday at Charlotte Maxeke Johannesburg Academic Hospital. Each patient will have to sign consent to allow their information to be used in this study. The questions posed will cover demographic information, details regarding onset of symptoms of Parkinson's Disease, and exposure to environmental toxins which have been previously linked to PD. The questionnaire will be followed by a mini-mental examination and their illness will be graded using the Modified Hoen and Yahr criteria. Once the data is collected it will be used to describe the general profile of our PD patients. The findings will then be compared to previous descriptions in Africa as well as Europe and North America.

(ii) Materials

Questionnaire

The questionnaire will include basic demographic information, including

- age,
- age of onset,
- race,
- gender
- level of education,
- occupation,
- toxin exposure,
- comorbidities,
- History of head injury,
- As well as clinical features such as tremor, pattern of rigidity, falls, posture.

The Modified Hoehn and Yahr scale (H&Y):

This is an IPD rating scale which broadly classifies areas of motor dysfunction in patients with PD. It is widely used. It was originally published in 1967[17]. It includes stages 1 to 5. Since then, a modified Hoen and Yahr scale was developed, which added stages 1.5 and 2.5[18]. These helped in describing the intermediate course of the disease. Of all the rating scales it is the most simple to apply. Progression in the H&Y score has been found to correlate closely with progression in physical disability. It focuses only on motor aspects of PD. The disadvantage of this test is that it fails to evaluate non-motor aspects of PD. Cognitive involvement in PD patients will be assessed using the Mini Mental State Examination.

Mini Mental State Examination:

The mini mental state examination (MMSE), also known as the Folstein test, is a 30-point questionnaire that is used extensively in clinical research to assess for cognitive impairment[19]. It was introduced by Folstein et al. in 1975, to help differentiate between organic and psychiatric patients. The MMSE is a simple and easily reproducible test for signs of cognitive impairment. Other advantages are that it requires no specialised equipment or training.

The test examines functions such as orientation, registration, attention, calculation, language, recall, and the ability to follow simple commands. Although it is not very sensitive for early signs of cognitive dysfunction, it has the advantage of not being culture specific. However, the test requires that the participant has a grade eight level of education, and is fluent in English. A MMSE score of less than 25 is considered as cognitive impairment.

Scwab and England Activities of Daily Living Scale:

This is another tool used to grade disability, in terms of how it impacts daily life[20].

Parkinson's Disease Questionnaire:

The questionnaire was designed to be simple to use as the examiner but also to be thorough enough to extract all the necessary information from patients. Wherever possible, questions are simplified so that an answer can be given as either a "yes" or "no" type questions or the answer can be selected from a list of possible answers. Symptoms and signs are graded in terms of severity on a scale of 1 to 5. This is all to ensure that data can be easily extracted and put into categories and that no information is left out.

(iii) Inclusion and exclusion criteria: All patients who attend the neurology and Movement Disorder clinics will be offered participation in the study. Included in the study will be patients previously or newly diagnosed with IPD, who have met the QSBB criteria for diagnosis of IPD.

Patients excluded in the study will be those who are known to have secondary PD i.e. as a result of a vascular event or use of neuroleptic drugs, or those with clinical features of a Parkinson's Plus syndrome.

Informed consent

All patients who qualify to participate in the study, with counselled as to the purpose of the study, confidentiality of medical information, and the right to refuse participation. Each participant will then have to sign a consent form in order to participate in the study. The consent form is attached.

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2. Appendices

Consent form for participation in the following study:

The Clinical profile of Idiopathic Parkinson's Disease in a South African Hospital Complex. A prospective Observational study.

Principal investigator: Dr M Smith
Supervisor: Prof. G Modi
Division of Neurology

I……..
understand that my participation in this study is voluntary and that the information will be kept anonymous. The details of the research process have been explained to me. I have had an opportunity to ask questions and have had them answered to my satisfaction. I hereby consent to participation in this research project.

Participant's signature……
Date…….

Witness ……

PARKINSON'S DISEASE RESEARCH

FACT SHEET

My name is Dr Marcelle Smith. I am a registrar in the Department of Neurology. I am doing my MMED research project on Parkinson's disease (PD). The study is entitled

"The Clinical Profile of Idiopathic Parkinson's Disease In A South African Hospital Complex. A Prospective Observational Study."

- The aim of this study is to understand the characteristics of PD in our population of patients that attend neurology clinics at Chris Hani Baragwanath Hospital and Charlotte Maxeke Hospital.
- The data collection involves completion of a questionnaire. This covers demographic information such as age, race, highest level of education, occupation and previous medical history.
- There are also questions concerning the PD itself, including time of diagnosis, family history, symptoms and signs and exposure to environmental toxins.
- The questionnaire is followed by a Mini Mental State Examination, which tests higher mental functions such as memory.
- Each participant then has their PD graded by the Hoen and Yahr scoring system followed by a disability scoring.
- The study does not involve any changes in treatment or any lab tests.
- Participation in this study is completely voluntary. Each person will be asked to sign consent before the information can be used. All information is kept anonymous. Each participants information is marked with a code which is made up of their initials and year of birth e.g. NM53 to ensure this.

For further information, please contact me on 011 488 4911

R14/49 Dr Marcelle Smith

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140712

NAME: (Principal Investigator)	Dr Marcelle Smith
DEPARTMENT:	Neurology Chris Hani Baragwanath Academic Hospital Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The Clinical Profile of Idiopathic Parkinson's Disease in a South African Hospital Complex. A Prospective Observational Study
DATE CONSIDERED:	25/07/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Girish Modi
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	13/01/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date 13/01/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

A. Parkinson's Questionnaire

1. Participant code:
2. Gender: ☐male ☐ female
3. Race: ☐ black ☐ white ☐ coloured
   ☐indian ☐ other, specify……
4. Highest level of education:
5. Dominant hand ☐ right ☐ left
6. Current/ previous occupation:
7. Family history of Parkinson's Disease ☐ Yes ☐ No
8. Social habits ☐ cigarettes ☐ alcohol ☐ caffeine ☐ illicit drugs, specify
9. Age of onset of symptoms:
10. Time taken for diagnosis to be made:
11. Side of first symptoms: ☐ Right ☐Left
12. Symptoms and signs
    - Tremor: 3-5Hz.☐ >5Hz.☐
    - Rigidity: Axial.☐ Appendicular.☐
    - Gait: Bradykinesia.☐ Festinating.☐ Magnetic .☐
    - Postural instability: Orthostatic hypotension.☐ Falling.☐
    - Posture: Erect.☐ Stooped.☐ Degree of kyphosis. ☐
    - Ocular: Abnormal saccades ☐ Impaired upgaze☐
13. Exposure to toxins- Heavy metals: ☐ iron ☐Manganese ☐Lead ☐copper
    ☐type unknown ☐other,
    specify……..
    - ☐pesticides/herbicides (paraquat ☐yes ☐no ☐unknown)
14. Psychiatric illness: ☐ no ☐ yes, type……..
15. Psychiatric medication: ☐ SSRI's ☐ TAD ☐ Antipsychotics
16. Previous head injury: ☐ yes ☐no
17. Previous stroke: ☐ yes ☐no

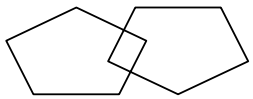
18. Other neurological diagnoses ☐ yes ☐no if yes, type……
19. Comorbidities ☐HPT ☐ DM ☐ Dyslipidaemia ☐none ☐other ……
20. PD treatment ☐ carbilev ☐ pexola ☐ symmetral ☐none ☐other, specify……
21. Are you satisfied with your treatment ☐ yes ☐no
22. Hoen and Yahr score

B. **Stage**	**Modified Hoehn and Yahr Scale**
☐1	Unilateral involvement only
☐1.5	Unilateral and axial involvement
☐2	Bilateral involvement without impairment of balance
☐2.5	Mild bilateral disease with recovery on pull test
☐3	Mild to moderate bilateral disease; some postural instability; physically independent
☐4	Severe disability; still able to walk or stand unassisted
☐5	Wheelchair bound or bedridden unless aided

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

***Instructions:* Ask the questions in the order listed. Score one point for each correct response within each question or activity.**

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

Schwab and England Activities of Daily Living Scale:

1. ☐100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
2. ☐90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
3. ☐80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
4. ☐70% = Not completely independent. More difficulty with some chores. Three to four times in some. Must spend a large part of the day with chores.
5. ☐60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Some impossible.
6. ☐50% = More dependent. Help with half, slower, etc. Difficulty with everything.
7. ☐40% = Very dependent. Can assist with all years, but few alone.
8. ☐30% = With effort, now and then does a few chores alone or begins alone. Much help needed.
9. ☐20% = Nothing alone. Can be a slight help with some chores. Severe invalid.
10. ☐10% = Totally dependent, helpless. Complete invalid.
11. ☐0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

3. RESEARCH ARTICLE

THE CLINICAL PROFILE OF IDIOPATHIC PARKINSON'S DISEASE IN A SOUTH AFRICAN HOSPITAL COMPLEX - THE INFLUENCE OF ETHNICITY AND GENDER

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Abstract:

Idiopathic Parkinsons Disease (IPD) has not been well studied in Black African populations. Data on the demographics, phenotype differences with Caucasoid populations, severity and frequencies of IPD in Black Africans is scant.

Aim: to determine the impact of ethnicity and gender on the phenotype of IPD in South African patients.

Method: Fifty patients with diagnosed IPD were recruited. The data collection was in the form of a questionnaire and clinical evaluation which included a mental status examination (MMSE), and illness staging.

Results: Thirty-five patients were Black African, eleven were white European descendant, three were of Indian descent and one had mixed ancestry. Twenty-eight of the patients were female. There were no significant gender differences within or between the different ethnic groups. Seventy- one percent of black and ninety-one percent of white participants had classic IPD presentations. A resting tremor was found in fifty-nine percent of all males in the study but in ninety-four percent of females. In the black IPD patients, thirty-one percent had early onset IPD (age of onset less than 50 years) with a gender ratio of M:F=1:6. Twenty-nine percent had an akinetic-rigid syndrome with erect posture and no tremor (gender ratio of M:F = 7:4) and seventy-four had cognitive impairment (gender ratio of M:F =8:5).

Conclusion: The phenotype of IPD in the majority of our study population is of the classic IPD type. In a third of our Black patients the onset was early and in a third the presentation was akinetic.

Keywords: Parkinsons disease; Gender; Ethnicity

Introduction

The classic profile of Idiopathic Parkinsons Disease is based on the data derived from European and North American populations. Little is known about IPD in people of African origin.

There have been a few studies investigating Idiopathic Parkinsons Disease in African American populations. In a study from Northern California, USA in 2003[1], the relationship between race and gender in patients with IPD was reported. The results showed an older age of onset in Whites compared to Blacks, Hispanics and Asians. The incidence of IPD was 91% higher in men than in women. A cross-sectional epidemiological study conducted across the USA in 2010[2] of US Medicare beneficiaries aged 65 and older, showed that there was a 50% lower incidence of IPD in Blacks compared to Whites.
In Africa, a systematic review reported from a Nigerian group in 2006[3] featuring articles that were published between 1944 and 2004 from 13 African countries, including South Africa concluded that the incidence and prevalence rates of IPD appeared lower in Africa than those in Europe and North America. In 2010, the same group published a study that investigated the clinical profile of Parkinsons Disease in a population of patients in Lagos, Nigeria[4]. These results were extracted from a data base collected over 10 years. Of the 124 patients with parkinsonism, 98 (79%) had Idiopathic Parkinsons Disease, while 26 (21%) had secondary PD. Results showed a similar disease profile to European counterparts, although there were fewer patients with early onset disease (<50 years old) (16.3%) and family history (1,.02%). In terms of clinical presentation, 31.6% were tremor- predominant, 55.1% were mixed, and 14.3% had an akinetic-rigid presentation. These different clinical presentations were not compared for gender. An important observation was that, compared to European studies, there was a greater delay in diagnosis. One of the negative aspects of this study was that patients with secondary Parkinsons disease were not excluded from the study.

The first study on IPD in the black South African population was published in 1988[5]. These results were derived from monitoring the prevalence of levodopa usage. The study concluded that IPD occurred less frequently in Black Africans. In terms of recent data, a study from Tygerberg Hospital in the Western Cape, South Africa, investigated the factors influencing the development of early onset (EOPD) or late onset Parkinsons Disease (LOPD), [6]. This data was extracted from a 5-year genetic study. Of the 397 patients, 62.5% (248) were male, and

34,8% (138) were female. Gender was found to have no effect on age of onset. EOPD was also found more frequently in Black, mixed-ancestry and White Afrikaner participants compare to white English speaking patients. This conflicts with the Lagos study's findings. A family history was associated with younger onset. However, one third of cases with LOPD had a significant family history.

No studies have looked specifically at whether there are different clinical phenotypes of IPD among different ethnic groups.

Aim:

The aim of this study was to determine whether ethnicity and gender have any influence on the clinical presentation of patients with IPD who attend the Neurology clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Hospital (CHBH) compared with the published European and North American clinical phenotypes.

Method:

Study design and study population:

This was an observational study conducted in two parts: a questionnaire and clinical evaluation.

The questionnaire (appendix 1) consisted of 22 questions pertaining to demographic information such as age, gender, race and clinically relevant history such as age of onset, family history, time to diagnosis, and the presence of specific symptoms.

The second component consisted of a series of clinical examination and a series of tests, namely, the Mini Mental State examination[7] (grading of cognitive impairment), the Hoehn and Yahr score [8;9] (grading of physical disability) and Schwab and England activities of daily living scale (S&E)[10].

The study population consisted of patients known with Idiopathic Parkinson's Disease who

attend the Movement disorder/ Neurology clinics at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Hospital in Johannesburg, South Africa. We offered participation to all the patients who visited the clinic during the study period.

Inclusion criteria:

A diagnosis of Idiopathic Parkinson's Disease (IPD) in keeping with the Queen Square Brain Bank (QSBB) criteria[11]. This is a universally accepted list of diagnostic criteria for IPD[12].

Able to give consent

Sufficient level of education to complete the MMSE

Exclusion criteria:

Secondary Parkinson's Disease due to neuroleptic drugs, vascular lesions.

Cognitive impairment too severe to enable consent for participation in the study

Refusal of participation

Features of a Parkinson's-Plus syndrome

A total of 50 patients met the inclusion criteria during the recruitment period.

The demographic and clinical data gathered was tabulated in an excel spread sheet and descriptive and inferential statistics we performed using SPSS software.

The findings were then compared to previous descriptions in Africa as well as Europe and North America.

For purposes of this study,

- Early onset Parkinson's Disease (EOPD) is defined, according to literature, as Age of Onset (AOO) of 50 years or younger.
- Cognitive impairment is defined as a MMSE score of less than 25.
- Erect posture is defined as an angle of spinal kyphosis less than 20 degrees, and a stooped posture as an angle of more than 40 degrees[13].
- Time to diagnosis will be abbreviated as TTDx.

Results:

50 patients were included in the study. Thirty-five (70%) were Black African, eleven (22%) were of European descent, three (6%) were of Indian descent, and one (2%) had mixed-ancestry. There was a slight female preponderance of 56%. The mean age of the participants was 63 years old (range 36-83). There were several clear trends that came to the fore when comparing race and gender groups. The clearest differences were in age of onset, posture, rigidity, and tremor. However, not all of the differences proved to be statistically significant.

Table 1: Demographic and illness staging differences.

	Black n=35				White n=11			P-value
	Mean	Range	95% CI		Mean	Range	95%CI	
Age	60.8	51-76	55,8:65,8	Age	67,2	44-83	61,6:72,8	0.089
AOO	54.31	12-78	49,6:59	AOO	60,7	43-78	53,5:67,9	0,164
TTDx	20,3	0-120	53.5-67.9	TTDx	56,7	0-360	22,8:136,3	0,33
MMSE	25	15-90	20.9:29:2	MMSE	24,6	13-30	20,9:28,3	1,0
H&Y	2,5	1-5	2,2:2,8	H&Y	2,45	1-5	1,6:3,3	0,75
S&E	61.8	10-90	53,6:70,0	S&E	66	20-90	43,1:89	0,51

AOO= age; TTDx= Time to diagnosis; MMSE= Mini mental state examination; H&Y= Hoen and Yahr score; S&E= Schwab and England activities of daily living scale.

Table 2: Descriptive analysis for black versus white patients.

	Symptom Prevalence		Significance of Difference		
	Black n(%)	**White n(%)**	**p-value**	**Likelihood ratio (LR)**	
Appendicular rigidity	**19 (54,3)**	**10(90,1)**	**0.033***	**5,95**	
Axial rigidity	28 (80)	4 (45,5)	0.34		
Stooped posture Erect posture	**11 (31,4)** **24 (68.6)**	**8 (72,7)** **3 (27.3)**	**0.039***	**4.3**	
Magnetic gait	32 (91,4)	0	1.0		
Festining gait	7 (20)	4 (36,4)	0.42		
bradykinesia	33 (94,3)	11(100)	1.0		
Falling	14 (40)	4 (36,40)	1.0		
Fam hx	3 (8,6)	2 (18,2)	0.58		
Tremor	9 (25,7)	100	0.42		
Orthostatic hypotension	5 (14,3)	0			

(* indicates statistical significance with a p-value of less than 0.05)

Table 3: Differences in symptom prevalence for gender.

	Male		Female		P-value
	Mean	95% CI	Mean	95% CI	
Age	60,1	53,2:67	64,6	60,3:68,9	0,4
AAO	56	50,5:61:5	56,5	51,1:61,8	0,9
TTDx	33,8	0,2:67,5	22	10,2:33,4	0,4
Mmse	26,4	19,5:33,3	24	22,6:25,3	0,42
H&Y	2,5	2:3	2,5	2,1:2,9	1,0
S&E	63,3	51,6:75,1	64,1	54,5:73,7	0,9
	Prevalence of clinical signs (%)		Comparison		
	Male	Female	p-value	LR	
Appendicular rigidity	63,6	64,3	0.79		
Axial rigidity	95,5	64,3	0.34		
Stooped posture	50	39,3	0.60		
Magnetic gait	5	7	1.0		
Festining gait	27,3	25	1.0		
bradykinesia	100	93,9	0.50		
Falling	36,4	42,9	0.60		
Fam hx	9	17,9	0.24		
tremor	**59,1**	**93,9**	**0.010***	**7.7**	
Orthostatic hypotension	0	4			

(* indicates statistical significance with a p-value of less than 0.05)

AOO= age; TTDx= Time to diagnosis; MMSE= Mini mental state examination; H&Y= Hoen and Yahr score; S&E= Schwab and England activities of daily living scale; Fam hx= Family history.

Table 4: Chief clinical differences found in this study.

	BLACK	WHITE
MEAN AAO	56,6	60,7
%EOPD	31	18
%COGNITIVE IMPAIREMENT	74	18
%AKINETIC-RIGID SYNDROME	29	9
%CLASSIC IPD	71	91

AOO= Age of onset; EOPD= early onset Parkinsons Disease.

Discussion

The aim of this study was to look at whether ethnicity and gender have a significant impact on the clinical presentation of Idiopathic Parkinson's Disease (IPD) in our patient population. To date, there have been no notable studies exploring possible differences in disease phenotype between Black and White patients.

Our study was conducted in a highly specialized clinic in a tertiary hospital, which serves a largely indigent population. As a result, we cannot draw conclusions on the prevalence of IPD, or differences in cognitive impairment. When comparing the different ethnic and gender groups, our study showed clear trends with regards to differences in phenotypes. The main differences seen were in age of onset, pattern of rigidity, posture and tremor.

Ethnicity:

The majority of patients in our study population had the classic presentation of IPD. This is a syndrome of late onset, resting tremor, stooped posture, appendicular rigidity, and bradykinesia. This included ninety-one percent of White and seventy-one percent of Black patients. However, a subset of patients, particularly Black patients, showed some deviations from the classic phenotype.

IPD is typically a disease of the elderly but modern literature describes an earlier disease onset in patients of African origin [1;6]. This was replicated in our study. One third of Black patients had early onset Parkinson's disease (EOPD) compared to eighteen percent of White patients.

Of note, Black patients were more likely to have axial (80%) rather than appendicular rigidity (54.3%) compared to White patients (45.5% and 90.1% respectively.) They were also more likely to have an erect posture (68.6%). These two findings were statistically significant (p-values= 0,033 and 0,039 respectively).

Furthermore, almost a third of Black patients had an akinetic-rigid presentation. This was particularly prevalent in Black males (54%).

There was a higher incidence of cognitive impairment in black patients. It is important to note that, although all participants had a sufficient level of education to complete the MMSE, there may have been some bias because of differences in the quality of education, a legacy of the

country's history of racial inequality. It is important to note that the MMSE has a culture bias and is not specific for features of a subcortical dementia, which is found in IPD. However, it is a good screening tool and is easily reproducible.

Gender:

There were also several differences in presentation between the two gender groups. There was a slight female preponderance of 56%, unlike the male preponderance described in literature. The clinical phenotype was similar between the two groups except for two marked differences. Firstly, the prevalence of axial rigidity was greater in males (95,5%) compared to females (64,3%). Secondly, the prevalence of a resting tremor was much higher in females (93,9%), compared to males (59,1%). This was statistically significant (p value= 0,01). The mean age of onset (AOO) was similar in male and female participants in both racial groups.

Conclusion

The phenotype of IPD in the majority of our study population is of the classic type. A third of our Black patients had EOPD. We identified a subset of Black patients (one third) who presented with an akinetic-rigid syndrome.

Although the results showed clear trends in the differences between race and gender groups, they were not all statistically significant. This is possibly due to the small sample size and hospital complex bias. A larger sample size and community study is needed to confirm these findings.

Limitations:

Our sample size was small and limited to one geographical area.

Although the recruitment time was sufficient, our sample size was biased by the fact that many patients at the movement disorder clinics had secondary Parkinsons disease. Several were too cognitively impaired to provide consent, and there were also many with insufficient schooling to perform cognitive testing.

The Hospitals in which the study was conducted serve more Black than White patients. As a result, more Black patients were recruited into the study.

The MMSE is a good screening tool but isn't designed for subcortical dementia which is found in IPD. It has a culture bias as well. MMSE scores have been shown to be lower in Black and other ethnic groups due to differences in English proficiency and socioeconomic factors[14].

A more expansive study is needed to validate our results.

Declaration:

No financial or material contributions to declare.

Acknoweldgements

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Figures:

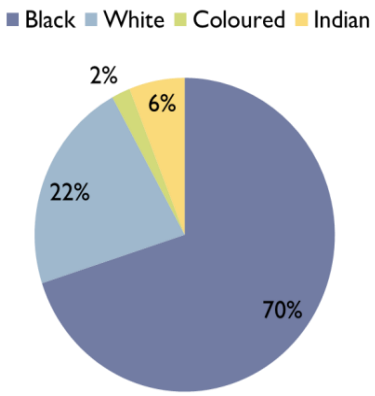

Figure 1: Ethnic distribution of sample.

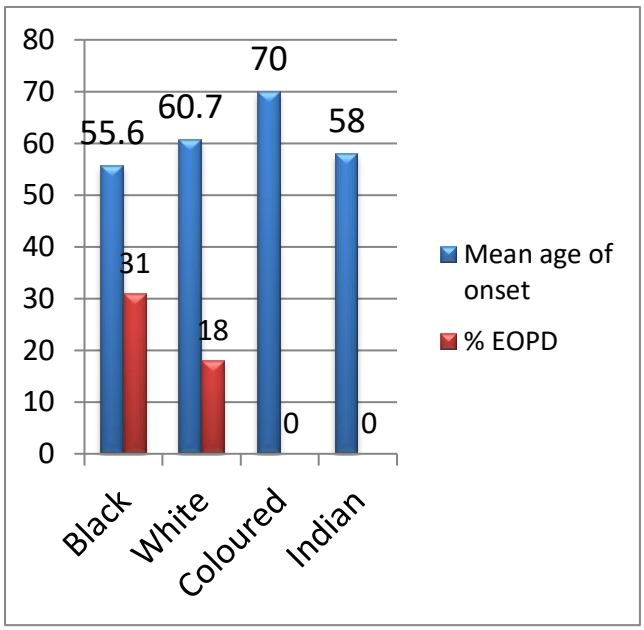

Figure 2: Mean age of onset.
%EOPD= percentage of early onset Parkinson's disease.

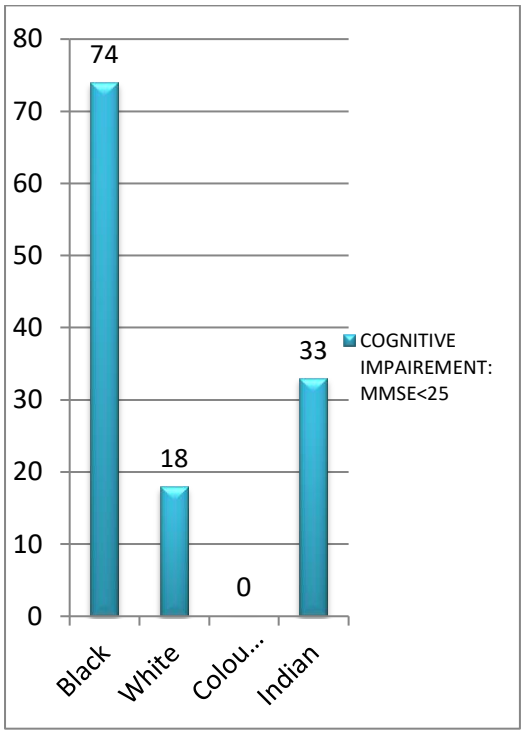

Figure 3: Percentage with cognitive impairment.
MMSE= mini mental state examination

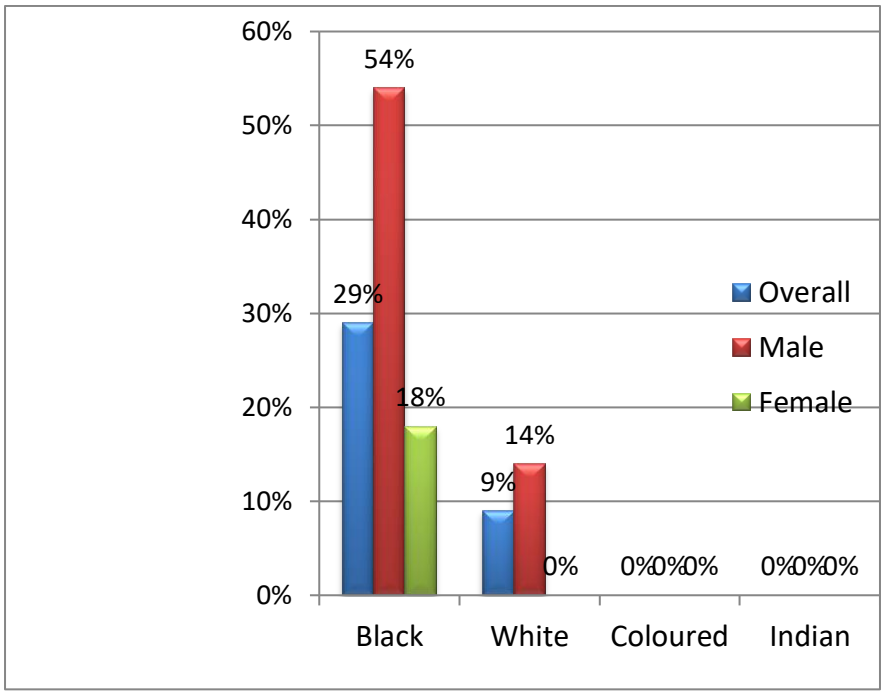

Figure 4: Percentage with Akinetic-rigid syndrome.

5. Corrections

1. Line 19: “criterion in” changed to “criterion is”
2. Line 22: “postural stability” changed to “postural instability”