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Phenotypic Characteristics of Zambian patients with Parkinson's Disease

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ABSTRACT

Objective: To describe the phenotypic characteristics of adult Zambian patients with newly diagnosed Parkinson's disease (PD) at University Teaching Hospital (UTH).

Background: The genetic basis of idiopathic Parkinson's disease is remains unknown. Little information is available regarding the genotype and phenotypic characteristics of PD among people of African origin.

Methods: Subjects with PD were recruited from the neurology clinic from January 2010, through April 2011. Parkinson's disease diagnosis was established according to standard criteria. Only ethnic Zambian patients were included to the study. The disease was considered familial when one or more first to third degree relatives were affected with PD. Extensive pedigree was constructed for all familial and sporadic cases. Unrelated healthy controls (spouses, volunteers) were free of PD and other movement disorders. Genomic DNA was extracted from peripheral blood leukocytes according to standard procedures from patients and controls, respectively.

Results: In total 46 patients for phenotype and 46 controls were matched with patients for age, gender, and area of residence. The mean age of patients at onset of the disease was 53.8 ±13.7years. Three patients had juvenile form PD and12 patients had early onset PD. In 31 patients the disease started after 50 years old. Tremor and bradykinesia were the most common initial symptoms. 26% had a history of first-and second-degree relatives affected with PD. Mean age were significantly lower in patients with familial PD (47.7±7.3) than sporadic disease (62,5±5.4) (p>0.001). In 8 families (66.6%) the disease had autosomal dominant and in 4 families (33.3%) autosomal recessive inheritance. Age at onset was significantly lower (27 years) in patients with autosomal recessive transmission than in patients with autosomal dominant inheritance. The disease duration was significantly longer in patients with autosomal recessive inheritance (11.2 years) than in patients with autosomal dominant inheritance (3 years).

Conclusions: This study represents phenotypic description of Zambian patients with PD recruited in clinical based manner. The majority of our patients were characterized tremor-dominant or akinetic-rigid types of the disease. Age at onset of PD was younger as compared to European population. The disease has both autosomal dominant and autosomal recessive inheritance. The familial aggregation of PD warrant further studies of genetic and environmental risk factors n the Zambian population

INTRODUCTION

The advances in the genetics of Parkinson's Disease (PD) is the most exciting, important development in the past 10 years since the first gene mutation in the disease, the gene for the protein alpha-synuclein[1] labeled PARK1(and SNCA), was identified. Since then, in the past decade, other genes have been mapped and many of them have also been identified[2,3,4] (Table 1).

Key words: Phenotype, Parkinson's disease, Zambian adults

Table 1. Genetic linkage and gene identification in PD

Name and locus	gene (symbol)
PRK 1, 4q21	α-Synuclein (SCNA)
PARK 2, 6q25.2-q27	Parkin (PRKN)
PARK3, 2p13	Unknown
PARK4, 4q21	Multiple copies of wild type SCNA
PARK5, 4p14	Ubiquitin-C-terminal hydrolase L1 (UCH-L1
PARK6, 1p35-p36	PTEN-induced kinase 1 (PINK1
PARK7, 1p36	DJ-1 (DJ-1)
PARK8, 12q12	Dardarin (leucine-rich repeat kinase2 (LRRK2)
PARK9, 1p36 (ATP13A2)	Lysosomal ATPase
PARK10, 1p32	Unknown
PARK11, 2q37.1	Unknown
PARK12, Xq21-q25	Unknown
PARK13, 2p12	Serine protease (HTRA2)
PARK14, 22q13.1 (PLA2G6)	Phospholipase A2
PARK15, 22q12-q13 (FBXO7)	F-box only protein 7
Glucocerebrosidase, 1q21	(GBA)
POLG1, 15q25 (POLG1)	Polymerase gamma

Most cases of PD are present in sporadic form, whereas a minority (~10-15%) are familial. A few of these families display either typical Mendelian autosomal dominant or recessive inheritance[5]. To date, mutations in five genes have clearly been associated with monogenic forms of PD providing new insights into the disease pathogenesis [5, 6]. Mode of inheritance is considered autosomal dominant for patients with mutations in SNCA and LRRK2 and autosomal recessive for patients with mutations in PRKN, PINK1 and DJ-1[7]. According to the recent study, 16% of enrolled 953 patients with early onset PD (below age 50) have a mutation in a known PD risk gene. These included 3% who were parkin homozygotes or compound heterozygotes (caring two different parkin mutations), 3% who carried a mutation in LRRK2, 6% who carried GBA mutations, and 1% who had mutations in two different genes. The proportion of known mutation carriers increased with decreasing age. Mutation carriers accounted for 15% of those between ages 30 and 50, 32% of those in their 20s, and 65% of those age 20 or younger. The authors suggest, the younger the age of onset, the better finding a genetic mutation. Most prevalence studies suggest that prevalence of PD is higher in whites than in non-whites and Africans are less likely have PD than whites[8,9,10]. Earlier and recently studies conducted in the USA showed that African-Americans were diagnosed with PD at half of the rate of whites[11,12]. According to the authors observed racial differences in incidence of PD were not explained by differences in age, sex, income, insurance or healthcare utilization but still may be explained by biological differences[12]. There are no investigations regarding prevalence of PD in many African (including Zambia) countries. Differences in prevalence between black and white patients may be the result of genetic or environmental risk factors or both, but it is critical to determine which. Molecular genetic studies performed in European[13-17], US[18,19,20], Latin American[21,22,23], Australian[24,25], Israelian[26,27], Iranian[28], Indian[29,30], Chinese[31-34], Japanese[35,36], Tunisian[37], and South Korean[38] patients, shows that genotypic differences more varies between populations and it depends very much on ethnic background. Up to date the majority of molecular genetic studies focused on the European, North American and Asian populations, and only one study on the investigation of the LRRK2 G2019S in South African PD patients[39].

The aim of the study was to describe the phenotypic characteristics of adult Zambian patients with newly diagnosed Parkinson's disease (PD) at University Teaching Hospital (UTH). This is an initial part of the multistage study on exploring genetic factors in PD in the adult Zambian population

PATIENTS AND METHODS

Subjects with PD were recruited from the neurology clinic. All patients were examined personally and followed up. Evaluation included standardized questionnaire and detailed neurological examination. In each patient were recorded: geographic and ethnic origin, sex, age, place of birth, age at onset and duration of the disease,

disease course from onset, medical history, dosage and duration of antiparkinsonian treatment. Parkinson's disease diagnosis was established according to standard criteria[40]. We only included cases of PD, and an effort made to exclude all other types of parkinsonism. Atypical features or signs of any akinetic-rigid. syndrome were not included to the study All proband's and patient's response to levodopa was evaluated by comparing untreated (i.e, after 24 hours levodopa withdrawal) and treated (i.e, after giving the patient a single dose of levodopa) Unified Parkinson's Disease Rating Scale (UPDRS) scores . "On" and "off" Hoehn and Yahr (HY) scores were determined . According to the literature[41,42] age of the patients classified as "early-onset Parkinson's disease" (EOPD) if the age at onset of the disease ≤40 years and ≥20 years, and "juvenile Parkinson's disease" if onset of the disease was before 21 years. (Brain CT or MRI scan were performed in 36 patients. All were normal. Unrelated healthy controls (spouses, volunteers) were free of PD and other movement disorders. Only ethnic Zambian patients were included to the study. All patients and control subjects signed informed consent. The study was approved by the Biomedical Research Ethics Committee, University of Zambia.

Familial history

Data on familial aggregation were collected from study participants during the screening phase of the survey, before any diagnostic procedure was performed.

Information about the presence of PD or similar cases, associated diseases among first degree and other relatives, current age or age at death and cause of death were obtained according to a structured questionnaire. The disease was considered familial when one or more first to third degree relatives were affected with PD. Extensive pedigree was constructed for all familial and sporadic cases. All sporadic cases made up a control group for familial cases. The sex ratio, transmission pattern, and ancestral secondary cases, and segregation ratio (SR) were determined by pedigree analysis. Familial PD classified as autosomal recessive (AR) inheritance when all affected members belonged to only one generation and autosomal dominant (AD) when affected members spanned more than one generation.

Statistical analysis. The SR was calculated according to the Weinberg Proband method, assuming multiple incomplete ascertainment. SR was estimated in each SG and MG families (total SR, SR for parents and for siblings). The Chi square test was used to test difference between SG and MG families sex ratio, categories of age at onset, initial symptom. The nonparametric Wilcoxon test was used to calculate differences in age, age at onset, disease duration, HY stages, and UPDRS scores.

RESULTS

The demographics and disease characteristics summarized in Table 2.

Table2. Demographic and disease characteristics

Characteristics	Total patient group	Spo radic	Familial
No of patients, n (%)	46	34 (74)	12 (26)
Gender, men/women	26/20	20/14	7/5
Age, yr Mean (SD)	59.2 (11.9)	62,5 (5.4)	47.7 (7.3)
Age at onset, mean (SD)	53.8 (13.7)	53.1 (8.2)	46,4 (7.5)
Age at onset 0-20, yr, n	3	1	2
Age at onset >20-30 yr, n	1		1
Age at onset >30-40 yr, n	1	1	
Age at onset >40-50 yr, n	10	7	3
Age at onset >50 yr, n	31	25	6
Disease duration, yrs, mean (SD)	5.4 (4.6)	5.7 (3.5)	6.7 (3.1)
Hoehn and Yahr score, n			
Stage I	4	4	-
Stage II	17	12	6
Stage III	21	16	5
Stage IV	4	2	1
Motor phenotype, n			
Tremor dominant	19	14	5
Akinetic-rigid	15	9	6
Non determinable	12	11	1

In total 46 patients, 26 men and 20 women, assessed for phenotype. A total of 46 controls (24males, 22 females) with the mean age 57.6±11.3 years were matched with patients for age, gender, and area of

residence. The mean age of patients was 59.2±11.9 years (range16-79). The mean age at onset was 53.8±13.7. Three patients had juvenile form PD whose disease started at 16 and 18 years old. Twelve patients had EOPD. The main age at onset of whom was 45,8±6.5 years (range 35-52). In 31 patients the disease started after 50 years old. They categorized as late-onset PD, the mean age at onset of whom was 59.8±9.7 years. Tremor and bradykinesia were the most common initial symptoms and most patients had tremor dominant type of the disease. 12patients (26%) had a history of first-and second-degree relatives affected with PD. Mean age 47.7±7.3 and age at onset 45.4±7.3 were significantly lower in patients with familial PD than sporadic disease (62,5±5.4 and 58.1± 8.2, respectively).

In 8 families (66.6%) the disease had autosomal dominant and in 4 families (33.3%) autosomal recessive inheritance. Age at onset was significantly lower (27 years) in patients with autosomal recessive transmission than in patients with autosomal dominant inheritance. The disease duration was significantly longer in patients with autosomal recessive inheritance (11.2 years) than in patients with autosomal dominant inheritance three years (3 years).

DISCUSSION

The majority of our patients were men and age at onset between 40 and 59 years was younger than in western cohort.[43] The majority of our patients, both men and women were characterized tremor-dominant or akinetic-rigid types of the disease, whereas a minority fell into the mixed category.Younger patients were more frequently tremor-dominant, whereas older patients were more likely to be subtyped as akinetic-rigid. Almost all patients showed slow progression of the disease and most of them classified as Hoehn and Yahr Stage 2 or 3. Although patients who are older at the time of PD onset and suffer from the akinetic-rigid type from onset progressing more quickly in comparison to patients with PD onset at younger age and suffer from the tremor-dominant type from onset. 26% of our patients reported a family history of PD in a first- or second degree relative which is higher than the range reported in European studies [44] .
Although this study find the aggregation of PD within Zambian families, it does not explain the contribution of genetic and environmental factors in this clustering.

The most significant limitation of the study is that its clinic-based design and small number of patients with PD.

Functional decline across time was observed in the majority of patients due to high cost of dopaminergic agents. Since UTH can provide only artane the most of our patients don't have access to adequate treatment for PD and the disease from the early stage is associated with substantial health and financial burden to families. There is no data on the prevalence of PD in Zambia and population based study is necessary to understand phenotypic characteristics of the disease and its burden in the country.

In conclusion, this study represents phenotypic description of Zambian patients with PD recruited in clinical based manner. The majority of our patients were characterized tremor-dominant or akinetic-rigid types of the disease. Age at onset of PD was younger as compared to European population. The disease has both autosomal dominant and autosomal recessive inheritance. The familial aggregation of PD warrant further studies of genetic and environmental risk factors n the Zambian population

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