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Parkinson's Disease in Sub-Saharan Africa: A Review of Epidemiology, Genetics and Access to Care

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Abstract

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A low prevalence of Parkinson's disease (PD) has been reported in the Sub-Saharan Africa (SSA) region. The genetic causes and clinical features of PD in this region have been poorly described. Very few reports have examined the availability and access to evidence-based quality care for people living with PD in this region. We reviewed all publications focusing on idiopathic PD from SSA published up to May 2016 and observed a prevalence of PD ranging from 7/100,000 in Ethiopia to 67/100,000 in Nigeria. The most recent community-based study reported a mean age at onset of 69.4 years. The infrequent occurrence of mutations in established PD genes was also observed in the region. Treatments were non-existent or at best irregular. Additionally, there is a lack of well-trained medical personnel and multidisciplinary teams in most countries in this region. Drugs for treating PD are either not available or unaffordable. Large-scale genetic and epidemiological studies are therefore needed in SSA to provide further insights into the roles of genetics and other etiological factors in the pathogenesis of PD. The quality of care also requires urgent improvement to meet the basic level of care required by PD patients.

Key Words: Parkinson's disease; Sub-Saharan Africa; genetics; epidemiology; access to care.

INTRODUCTION

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Sub-Saharan Africa (SSA) is composed of African countries south of the Sahara and consists of 47 politically distinct states. SSA is one of the fastest growing regions of the world, with significant economic growth in the past 10–15 years, which has reflected in a greater availability of and access to health facilities. However, most countries in the region are still below the World Health Organization (WHO) standard of one doctor per 100,000 population [1]. The population of those with Parkinson's disease (PD) in the SSA region is known to be relatively small. The low prevalence of PD in SSA may stem from several issues, including the relatively youthful population in SSA, with less than 5% of the total population above 65 years; the fact that most cases of PD are not recognized partly because of the assumption that neurological diseases are part of normal aging; and the scarcity of epidemiological studies in SSA [2].
Key aspects of PD, such as the incidence and prevalence, genetic causes and clinical presentation, are poorly characterized in SSA [3]. Few reports have examined the availability of and access to evidencebased quality care for people living with PD in SSA countries.
This review aims to accomplish the following:
1) Provide a descriptive summary of all epidemiologic and genetic studies from SSA published up to May 2016.
2) Compare the genetic and epidemiologic results from SSA to those from other populations in Africa outside SSA.
3) Review the level of care available and accessible to PD patients in SSA.

MATERIALS & METHODS

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Inclusion criteria

This review included all population-, outpatient clinic- and in-patient-based studies investigating epidemiologic, genetic or care-related aspects of PD in SSA up to May 2016. Only studies focusing on idiopathic PD using either the UK Parkinson Disease Society (UKPDS) brain bank [4] or the WHO or Movement Disorders Society (MDS) diagnostic criteria [5] were included.

Exclusion criteria

Only studies published in English were included. Articles on neurological inpatients or outpatients that did not focus on PD frequencies were excluded. We excluded review articles, with the exception of their references.

Search methods

Electronic searches

Electronic databases, such as MEDLINE and African journals online, were used as the initial search resources. To include all relevant publications within the scope of this review, the search was extended to include the following:
1) Reference lists of all review articles and primary studies available.
2) References found in abstract books of the European Federation of Neurological Societies (EFNS), American Academy of Neurology (AAN), MDS, and Pan-African Association of Neurological Societies (PAANS).
3) References lists of relevant textbooks and citations of PD studies in Africa.
If articles investigating the treatment available for PD patients in SSA were not found in the initial search resources, the search was extended to include available WHO and World Bank data containing statistics on health care personnel and facilities in different regions of the world. Websites of the MDS Africa task force, patient support groups (Parkinson's Disease Association) and professional organizations (e.g., speech and language therapy and occupational therapy) in Africa were also searched for available relevant services. Reports of PD-related services were also evaluated in this review. The flow diagram of the search process is shown in Figure 1.

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Data collection and analysis

Study selection

The titles and abstracts obtained from the electronic database search were reviewed, and irrelevant studies were excluded. Full copies of the relevant studies were obtained and reviewed in detail.

Data extraction

Relevant information from the studies was obtained using a data extraction sheet. The information sought included year of study, authors, country, setting of study, duration of study, year of publication, type of study, number of subjects, study design, characteristics of participants [age, gender, age at onset, duration of disease, Hoehn and Yahr rating, UPDRS (unified Parkinson's disease rating scale) score, family history of PD], description of the study, and diagnostic criteria used. For prevalence studies, the crude prevalence and age-adjusted prevalence were recorded where available and reported as the number of patients per 100,000 persons. In the case of genetic studies, information regarding the genes studied, genetic mutations found, and the method for genetic analysis used was also extracted. Studies in other populations with similar characteristics were reviewed for prevalence statistics for comparison with those obtained in SSA.

Data analysis

Data analysis was performed using Microsoft Excel, and the results are presented in the text, figures and tables.

RESULTS

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We identified 11 genetic studies, 7 communitybased (door-to-door) prevalence studies and no incidence studies in SSA populations. The genetic studies were all undertaken within the past decade. Regarding the distribution of genetic studies, 7 were from South Africa and 1 each was from Nigeria, Zambia and Ghana. One study [6] included samples from the Human Diversity series extracted from different countries in SSA, including Nigeria, the Central African Republic, the Democratic Republic of the Congo, Kenya, Namibia, Senegal and South Africa. The first genetic study was conducted by Okubadejo et al. [7], in which they screened 51 Nigerians with sporadic PD and an equal number of controls for mutations in leucine-rich repeat kinase 2 (LRRK2), parkin (PRKN) and ataxin 3 (ATXN3). They concluded that pathogenic mutations in these genes were not common in Nigerians. Studies from South Africa examined mutations involving eukaryotic translation initiation factor 4GI (EIF4GI), vacuolar protein sorting 35 (VPS35), Parkin, microtubule-associated protein tau (MAPT), synuclein alpha interaction protein (SNCAIP), PTEN-induced putative kinase 1 (PINK1), LRRK2, SNCA, PINK1, DJ-1, ubiquitin carboxyl-terminal esterase L1 (UCH-L1), ATP13A2, LPA, TNFSF9, CAV2, CAV1, and GCH1 [8-12]. These studies concluded that mutations in these genes are not a common cause of PD in the South African population.
The Ghanaian study analyzed mutations in the LRRK2 gene, while that from Zambia screened all the SNCA, LRRK2, PINK1, DJ-1, and Parkin exons for any pathogenic mutations. Interestingly, these studies did not detect any pathogenic mutations among the indigenous black PD patients compared to other populations in which mutations in these genes have been associated with either sporadic or familial PD. The findings from these genetic studies are summarized in Table 1 and 2.

Table 1.
Genetic studies in SSA

S/N	Genetic mutation studied	Method of analysis	Result(s)	Sample size	Country (Reference)
1	LRRK2, PRKN, ATXN3	Analyzed for common mutations using the Oragene kit for DNA extraction (DNA genotek)	No pathogenic mutations were found.	51 PD patients & 51 controls	Nigeria (Okubadejo et al. [7])
2	Parkin	Single-strand conformation polymorphism analysis and the HRM* technique	• Four disease-causing missense heterogeneous changes (H200Q, D280N, E310D, R4026) • Two homozygous exon deletions (exon 3 & 4)	91	South Africa (Bardien et al. [42])
3	LRRK2	HRM	• LRRK2 G2019S mutation found in 2 patients	205	South Africa (Bardien et al. [12])
4	SNCA, Parkin, PINK1, DJ-1, LRRK2, UCH-L1, ATP13A2	MLPA†	• Exonic rearrangement in Parkin & SNCA in 7 (8%) patients • No exonic rearrangement	88	South Africa (Keyser et al. [11])

			in 4 genes (LRRK2, PINK1, DJ-1, & ATP13A2)		
5	PINK1	HRM technique & direct sequencing	• Sixteen variants found: - One homozygous mutation (Y258X) - Two heterozygous missense variants (P305A & E476K) - Thirteen polymorphisms, of which five were novel.	154	South Africa (Keyser et al. [11])
6	MAPT, SNCAIP	HRM method	• Two novel variants found for MAPT • One previously sequenced variant (E709Q) and three novel missense variants of SNCAIP	202	South Africa (Keyser et al. [10])
7	E1F4G1‡ (NM_182917.3)	PCR amplified & sequenced	• EIF4G1 coding variants found in the SSA population were M290I, R305C, Y311C, P382L, E477K, & R1216H.	127 (SSA samples from the Human Diversity series)	Sample from the Central African Republic, the DR of the Congo, Kenya, Nigeria, Namibia, Senegal, and South Africa (Tucci et al. [6])
8	SNCA, LRRK2, PINK1, DJ-1, Parkin	Direct sequencing	• Pathogenic mutation not detected in SNCA, PINK1 or DJ-1 • Novel LRRK2 missense variant detected in one case • Two heterozygous likely disease-causing deletions of Parkin (exon 2 & 4) detected in early-onset cases	39	Zambia (Yonova-Doing et al. [43])
9	Parkin	HRM and MLPA	• Seven patients compound mutation in Parkin gene • Seven patients had heterozygous sequence variants	229 PD patients and ethically matched controls	South Africa (Haylett et al. [9])
10	LRRK2	Direct sequencing	LRRK2 exon 41 & 31 screening did not detect any mutations in all samples.	54 PD patients and 46 controls	Ghana (Cilia et al. [53])
11	EIF4G1, VPS35‡	KASP genotyping assay	No mutations found	418 PD patients & 528 controls	South Africa (Blanckenberg et al. [3])

* HRM is a sequencing screening used to detect genetic variations due to processes such as mutation and polymorphisms,
† MLPA is a technique used to detect exon dosage changes caused by genomic rearrangements,
‡ E1F4GI and VPS35 are not among the well-established genetic causes of PD and have been suggested to be involved in its etiology, MLPA: multiplex ligation-dependent-probe amplification, SSA: Sub-Saharan Africa, HRM, high-resolution melt, PD: Parkinson's disease, KASP: kompetitive Allele Specific PCR, E1F4GI: eukaryotic translation initiation factor 4GI, VPS35: vacuolar protein sorting 35.

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Table 2.

Novel gene variants found in Sub-Saharan Africa studies

S/N	Novel genetic variant(s)*	Gene	Country	Reference
1	Heterozygous variant of PRKN (p.R334H and p.A46T)	*PRKN*	Nigeria	Okubadejo et al. [7]
2	H200Q in exon 5 in a patient with a family history of PD E310D in one patient with PD	*Parkin*	South Africa	Bardien et al. [42]
3	P305A variant reported in a female patient of a black Xhosa family with a positive family history of PD. Age at onset of 30 years.	*PINK1*	South Africa	Keyser et al. [11]
4	Two novel variants found for MAPT reported in two patients. A91V in a male of mixed ancestry, with age at onset of 32 years. V6351 in a black male with age at onset of 60 years. Both variants predicted by PolyPhen as being benign variants.	*MAPT*	South Africa	Keyser et al. [10]
5	Novel LRRK2 missense (p.Ala1464Gly) of questionable pathological significance detected in one PD patient	*LRRK2*	Zambia	Yonova-Doing et al. [43]

* novel variants-potential disease-causing mutations found in PD patients but not in controls.
PD: Parkinson's disease.

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The fact that these mutations were not observed in any of the genetic screens in SSA suggests that PD in SSA may have a unique genetic heritage. The genetic architecture of the indigenous people of SSA appears to be different from that of other populations outside Africa and in parts of Africa outside SSA. Despite the progress made in the past decade in PD genetics in SSA, it remains largely unexplored despite offering potentially one of the greatest diversity of polymorphisms that can be studied in any region of the world.

Prevalence of PD in SSA

The first epidemiological studies on PD in SSA were undertaken in the 1980s in Nigeria, Ethiopia and Togo, and the most recent studies were community-based prevalence studies from SSA, as summarized in Table 3. The prevalence of PD in these studies ranged from 7/100,000 in Ethiopia to 67/100,000 in Nigeria. Data from the World Bank regarding the estimated proportion of the country older than 65 years at the times these studies were conducted are similar, suggesting a similarity in population structure in the different SSA countries studied [13]. The first large-scale community-based prevalence study of PD was undertaken by Dotchin et al. [14] This study investigated a population of 161,071 community dwellers using a two-stage procedure that involved 6 initial screening sessions followed by an expanded history and neurological examination of positive responders to confirm the diagnosis of PD. They utilized the UKPDS brain bank criteria for the diagnosis of PD [4,15]. The age-adjusted prevalence was 40/100,000, which is lower than figures from Sweden and the United States, which were 76/100,000 and 1036-2168/100,000, respectively [16,17].

Table 3.
Community-based (door-to-door) prevalence studies in Sub-Saharan Africa

S/N	Country	Year	Population size studied	Percentage of population > 65 years at the time of study*	Diagnostic criteria/ study procedure	Prevalence	Reference
1	Nigeria	1982	20,000 rural community dwellers	3	WHO research protocol*	10/100,000	Osuntokun et al. [54]
2	Nigeria	1987	3,412 rural community dwellers	3	WHO research protocol	2/3,412 (0.1%) Age-adjusted prevalence ratio = 67/100,000	Schoenberg et al. [55]
3	Ethiopia	1986 to 1988	60,820 community dwellers	3	Not stated	7/100,000	Tekle-Haimanot et al. [56]
4	Togo	1989	19,241 residing in two rural settings	3	WHO research protocol	20/100,000	Balogou et al. [44]
5	Tanzania	2003	16,647 rural community	3	UK PD Society Brain Bank Criteria†	Diagnosis of PD not confirmed in any of the patients	Winkler et al. [31]
6	Tanzania	2006	161,071	3	UK PD Society Brain Bank Criteria	33/100,000	Dotchin et al. [14]

* estimated proportion of people > 65 years at time of study was obtained from the World Bank data base records, World Bank, 2014,
† UK PD brain bank criteria require the presence of bradykinesia plus at least one of rigidity, tremor or postural instability,
‡ WHO protocol: This is a 2-stage procedure involving initial screening with a questionnaire followed by clinical examination by a specialist.
PD: Parkinson's disease.

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Hospital-based studies

Several clinic- and hospital-based studies have estimated the frequency of PD in SSA among medical admissions, neurological admissions, or neurology clinic attendants. Unlike community-based studies, most hospital-based series are recent surveys undertaken within the last 10 years. The hospital frequency depends on the setting in which it was estimated, as in-patient-based admission estimates are lower than ones from outpatient-based studies. Only two admission-based studies were identified. Talabi [18] reported that PD accounted for 0.5% of all neurological admissions in a Nigerian hospital, while Lombard and Gelfand [19] reported that PD was responsible for 0.02% of admissions among black populations in a Zimbabwean hospital between 1973 and 1976. Outpatient-based studies reviewing hospital records of consecutive referrals to neurology clinics provided estimates of PD frequency among neurology referrals or patients with Parkinsonism. The outpatient-based series and the estimated hospital frequency of PD studies and their references are summarized in Table 4.

Table 4.
Outpatient clinic-based studies in Sub-Saharan Africa

S/N	Country	Year*	Patient group studied	Diagnostic criteria	Hospital frequency	Reference
1	Cameroon	2005-	912 neurological consultations in	UK PD	2.96% of all neurology referrals	Tegueu et

		2011 (6 yrs)	the outpatient clinic	Society Brain Bank Criteria		al. [57]
2	Cameroon	1993-2001 (9 yrs)	84 patients referred to the outpatient clinic with degenerative brain disease	Same	48.8% of all patients referred with degenerative brain disease	Kengne et al. [58]
3	Ethiopia	2003-2004 (1 yr)	720 neurological referrals to the outpatient clinic	NS†	7.2% of all neurological referrals to the outpatient clinic	Bower et al. [34]
4	Nigeria	1996-2006 (10 yrs)	1,360 new referrals to the outpatient neurology clinic	UK PD Society Brain Bank Criteria	1.47% of all referrals to the clinic	Okubadejo et al. [59]
5	Tanzania	2002-2006 (4 yrs)	1,908 consecutive referrals to the outpatient neurology clinic	UK PD Society Brain Bank Criteria	2.2% of all neurological referrals	Matuja and Aris [60]
6	Zambia	1999-2004 (5 yrs)	163 patients who visited the OPD or were admitted with extrapyramidal symptoms	NS	31.3% of all referrals to neurology clinic or admitted to hospital with extrapyramidal symptoms	Atadzhanov and Mwaba [20]

* the duration of review varies between the different studies from 1 year to 10 years,

† NS indicates that the diagnostic criteria were not clearly stated in the study concerned.

PD: Parkinson's disease.

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Clinical characteristics of the different cohorts of patients studied in the sub-Saharan Africa studies

Dotchin et al. [14] reported a mean age at disease onset of 69.4 years in the most recent communitybased population prevalence survey. The age of the patients at the time of these studies ranged from as young as 17 years, reported by Atadzhanov and Mwaba [20], to as old as 94 years, reported by Dotchin et al. [14] These studies, in keeping with reports in other populations outside SSA, observed a male preponderance, with a male-to-female ratio ranging from 1.2:1 to 4:1.

Evaluation of available care for PD patients in SSA

Evaluating the care of patients with PD in SSA is very challenging, as there are no systematic studies evaluating the care available or accessible to PD patients in this area. This review compares the availability of personnel, drugs and facilities in different settings to that recommended by standard guidelines such as the National Institute for Health and Care Excellence (NICE) [21] or the Canadian guidelines for PD [22].

Availability of standard management for PD patients in SSA

Neurologists

The lack of neurologists and movement disorder specialists has made it difficult to diagnose and treat PD patients properly in SSA. Documented estimates of country medical and neurological resources reported in the WHO atlas of country resources for neurological disorders [23] and WHO reports [1] indicate that there are 0.03 neurologists per 100,000 population compared to 0.07 in South East Asia and 4.84 per 100,000 population in Europe. Looking at the mean average of neurologists for all SSA countries does not portray the real deficiencies in the different countries. A typical example is Malawi, where it was reported that until recently, there was only one part-time neurologist for a population of approximately 12 million people [24].

Moreover, the number of geriatricians was small in SSA, with over 30 countries having no undergraduate or postgraduate geriatric training scheme [25].

Parkinson's disease nurses

PD is a new field of specialization in the region, as the first ever PD nurse training program in the region was led by Louise Ebenezer, a PD nurse specialist from the United Kingdom, in Tanzania in December 2012 with participating nurses from Rwanda, Uganda, Ethiopia, Kenya, Nigeria and Tanzania [26,27]. Subsequent courses have been held in Anglophone West Africa (Ghana 2013), Southern Africa (South Africa 2014) and Eastern Africa (Ethiopia in January 2016). WHO data show that there were no neurology nurses as of 2006 in SSA per 100,000 population compared to 0.005 in Southeast Asia, 0.13 in the Eastern Mediterranean, 0.14 in the Americas, 0.32 in the Western Pacific and 2.43 in Europe per 100,000 population at the same time [23].

Speech-language therapist

The presence of speech-language therapist (SLT) services in each country from SSA was assessed to evaluate their availability. A search of the SSA regional SLT website suggests that no SLT services have been registered in the following countries: Burundi, Burkina Faso, Cape Verde, Gambia, Guinea, Guinea Bissau, Liberia, Mali, Niger and Sierra Leone.

SLT services are available in Kenya, Rwanda, Tanzania and Uganda in East Africa and in Cote d'Ivoire, Ghana, Nigeria, Senegal and Togo in West Africa; additionally, training is available at Kampala, Uganda, and at several universities in South Africa, including the university of Pretoria, Witwatersrand, Limpopo, Cape Town, and Stellenbosch [28].

Occupational therapy and physiotherapy

No regional studies have evaluated the availability or benefit of occupational therapy (OT)/physiotherapy (PT) services among Africans with PD. Active OT services are, however, currently registered in Botswana, Kenya, Malawi, Mauritius, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, and Zimbabwe [29]. For example, Nigeria had only 3 registered occupational therapists out of 160 million people [23]. As of 2006, WHO data suggest that neuro-rehabilitation services are generally present in 81.2% of countries in Africa [1]. Dotchin et al. [30] reported that none of the PD patients reviewed in their series had visited a physiotherapist, while only one patient had seen an occupational therapist.

Availability of drugs

Most patients in SSA with PD do not have access to PD medication due to unavailability or, where available, financial constraints. PD drugs are available in only 12.5% of Africa, mostly in North Africa and South Africa, compared to 79.1% in Europe [23]. Indeed, studies from SSA referring to the availability of PD drugs indicate that procurement of Parkinsonism drugs remains a difficult task. Winkler et al. [31] stated that local pharmacies did not store L-dopa. Furthermore, the nearest pharmacy with a supply of L-dopa available was approximately 300 km away, thus introducing the additional cost of transportation, which most of the patients could not afford. In northern Nigeria, only 250/25 mg of L-dopa was available to PD patients [32]. Patients in their study who were able to afford ropinirole, pramipexole and selegiline had these medications brought in from either the Middle East or Asia. Cubo et al. [33] compared the clinical profile of PD patients in Spanish and Cameroonian cohorts. They observed that the Cameroonian patients were intermittently treated, received L-dopa at lower doses, had less access to DAs, and used anticholinergics more frequently. The use of selegiline, rasagiline and DAs was noted mostly in the Spanish cohort. Bower et al. [34] evaluated the adequacy of treatment of PD patients seen in a movement disorders clinic in Ethiopia and reported that only 59.6% of their patients received adequate L-dopa over the study period.
Dotchin et al. [35] investigated levodopa plus carbidopa use in a three-year follow-up study in Hai in rural Tanzania. They reported that MAO-B inhibitors and non-ergot DA were unavailable to PD patients. Bromocriptine, an ergot DA, was available as it was on the essential medicines list for the treatment of infertility. Ogunniyi [36], in his review titled, “Treatment of Parkinsonism syndromes in developing countries,” observed that anticholinergics are among the most commonly used drugs and that the use of DAs is limited due to their high cost. Overall, the literature suggests that even when patients are able to be diagnosed with PD, treatment is irregular or non-existent, monitoring is limited, people resort to local traditional healers for treatment, and multidisciplinary staff are rarely available [30]. Mokaya et al. [37] evaluated 48 drug outlets in Kenya and reported that only 24 outlets, one of which was a public pharmacy, had L-dopa. Ergot-derived DAs and anticholinergics were sold in 37 and 35 outlets, respectively. Catechol-O-methyl transferase inhibitors were not available in any of the outlets.

The cost burden of PD management in SSA

Although the estimated cost burden of the treatment of PD varied by country, it was generally accepted that the cost burden was comparably high, making it difficult for most PD patients in SSA to maintain treatment. In Tanzania, Mshana et al. [38] estimated that a one-month supply of PD drugs cost approximately 40,000 Tanzanian shillings, which is equivalent to approximately 33 US dollars (USD). In Ethiopia, Bower et al. [34] reported that a monthly dose of 25 mg/250 mg levodopa/carbidopa cost an estimated 90 Ethiopian birr, which is equivalent to 10.49 USD, and that the cost of an outpatient visit was approximately 0.66 USD. In Kenya, 100 tablets of L-dopa cost between 28.2 and 82.4 USD, with a mean cost of 48.2 USD [37].
In many SSA settings, patients also pay for their transportation and for the consultation, thereby increasing the cost of PD care [39]. Cilia et al. [40] observed that when they compared Ghanaian and Italian PD patients, levodopa was introduced to patients in Ghana later than to the Italian patients.
Neurosurgery and neuroradiology services
The estimated median number of neurosurgeons per 100,000 population is 0.01 in Africa compared to 1.02 in Europe and 0.39 per 100,000 population in the Western Pacific [23]. Femi et al. [32] reported that there were no neurosurgical services available for PD patients in a hospital-based clinical series in Nigeria. Cubo et al. [33] reported that a lack of imaging facilities impaired their ability to differentiate secondary Parkinsonism from idiopathic PD among the patients they were evaluating in Cameroon. Dechambenoit et al. [41], in his paper “Action Africa,” described a lack of equipment and outdated operating theaters, with an absence of instruments for microsurgery and microscopes. He further stated that where neurosurgery institutes were available, they were inaccessible to 90% of the population due to a lack of health insurance systems. He also expressed the view that the prevailing economic conditions in SSA underlie the difficulties in equipping neurology and neurosurgical services, as well as the training of young doctors. His views regarding the lack of neuroimaging services were supported by Dotchin and Walker [39], who reported that dopamine transporter imaging, which is useful in differentiating PD from other tremor disorders, is unavailable in all settings in SSA. A summary of available standard management of PD patients in SSA is presented in Table 5.

Table 5.
Summary of available standard management for PD patients in SSA

Item	Key finding(s)	Reference(s)
Availability of neurologist	- 0.03 neurologists per 100,000 population in SSA compared to 0.07 in South East Asia and 4.84 per 100,000 population in Europe.	- WHO [23]; WHO [1]
	- Until 2009, only one neurologist in Malawi with a population of 12 million.	- Jung et al. [24]
Availability of geriatricians	- Limited number of geriatricians	- Dotchin et al. [25]
	- No undergraduate & postgraduate training scheme in over 25 countries.	
PD Nurses	- No neurology nurses in SSA as of 2006.	- WHO [23]
	- First PD nurses training occurred in 2012.	- Walker [26]; Walker et al. [27]
Speech-language therapist (SLT)	- No SLT services in Burundi, Burkina Faso, Cape Verde, Gambia, Guinea, Guinea Bissau, Liberia, Mali, Niger or Sierra Leone.	- Speech-Language Therapy.COM; ASHA.org. [28]
OT and PT	- No regional studies evaluating OT/PT.	- History of OTARG to 2012 [29]
	- Active OT services registered in Botswana, Kenya, Malawi, Mauritius, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, and Zimbabwe.	- WHO [23]
	- Only three registered occupational therapists caring for 160 million people.	- WHO [1]
	- Neuro-rehabilitation services present in only 81.2% of countries in SSA.	
Availability of drugs	- In Africa, PD drugs mainly available in 12.5% of countries mostly in North Africa & South Africa compared to 79.1% in Europe.	- WHO [23]
	- Local pharmacies do not store levodopa in Tanzania.	- Winkler et al. [31]
	- Only 250/25 mg preparation of L-dopa available in Nigeria. Ropinirole, Pramipexole and Selegiline rarely available in the country.	- Femi et al. [32]
	- Cameroonian patients have little access to dopamine agonist.	- Cubo et al. [33]
	- Only 59.6% of Ethiopian patients had adequate L-dopa.	- Bower et al. [34]
	- Monoamine oxidase B inhibitors and non-ergot dopamine agonist not	- Dotchin et al. [35]

	available in rural Tanzania.	
	- Catechol-O-methyl transferase inhibitors were not available in any of the outlets in Kenya.	- Mokaya et al. [37]
Cost of PD care	- Estimated cost of PD drug for one month in Tanzania was 33 US dollars.	- Mshana et al. [38]
	- Monthly cost of 250/25 mg levodopa/carbidopa in Ethiopia was 10.49 US dollars, while the cost equivalent of an outpatient visit was approximately 0.66 US dollars.	- Bower et al. [34]
	- In Kenya, the average cost of 100 tablets of L-dopa was between 28.2 and 82.4 US dollars with an average of 48.2 US dollars.	- Mokaya et al. [37]
	- PD patients have the added cost burden of paying for their transportation and consultation.	- Dotchin and Walker [39]
Neurosurgery & Neuroradiology Services	- There are 0.01 neurosurgeons per 100,000 population in Africa compared to 1.02 in Europe and 0.39 per 100,000 population in Western pacific.	- WHO [23]
	- No neurosurgery service for PD patients in Nigeria.	- Femi et al. [32]
	- Lack of neuroimaging service in Cameroon.	- Cubo et al. [33]
	- Dopamine imaging facility not available in SSA.	- Dotchin and Walker [39]

PD: Parkinson's disease, SSA: Sub-Saharan Africa, OT: occupational therapy, PT: physiotherapy.

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DISCUSSION

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Genetics of PD in SSA

The findings of this review support the view that there is a possible unique genetic architecture of PD in the region because of the infrequent occurrence of mutations in established PD genes in SSA. This interpretation must, however, be viewed in the context that most of the studies in SSA had small sample sizes, with the largest being 205 subjects [12], which makes the generalization of their findings difficult. The likelihood of discovering mutations in PARK genes might increase if considerably larger PD cohorts from SSA were to be analyzed. The identification of mutations in established PD genes was documented only for *Parkin* among South African and Zambian cohorts from the 11 studies reviewed [9,42,43]. Both homozygous exon deletions [9,43] and point mutations [9,42,43] were observed in these studies. No pathogenic mutations were documented in studies screening for universally recognized PD genes such as α-synuclein, *LRRK2, PINK1* and *DJ-1* or genes of uncertain significance such as UCHL-1 in sub-Saharan PD cohorts. The mean age at onset in most of the patients studied was above 50 years, while mutations in PD genes are more commonly found in early-onset PD, especially mutations in autosomal recessively inherited genes such as *Parkin, PINK1* and DJ-1.

Epidemiology

This review has described different rates of occurrence in both hospital- and community-based studies. Balogou et al. [44] reported a prevalence rate of 20/100,000 in their study, but Winkler et al. [31] found no cases of PD among 1,569 community dwellers screened in rural Tanzania. The findings from other populations are significantly higher than those reported in SSA. Seo et al. [45] in Korea reported a prevalence of 374/100,000 people > 18 years, while a prevalence of 146/100,000 was reported in Australia [46]. These findings are very close to those of different European studies, such as the prevalence of 144/100,000 in Wales [47], 128/100,000 in England [48] and 166/100,000 in Finland [49]. Mayeux et al. [50] published a slightly lower prevalence of 107/100,000 in the United States of America. The lower prevalence of PD in SSA could be due to different study methodologies and diagnostic criteria; the lower proportion of those older than 65 years in the SSA population; reduced access to health care; different health-seeking behavior in the region; disease-related disability and cultural differences in the studied populations [3]; or the underdiagnosis of PD due to low social recognition, as typical symptoms of PD might be mistaken for symptoms of normal aging [51]. Blanckenberg et al. [3] suggested that the decreased survival of PD patients due to a lack of drugs, unavailability of proper health care and other socio-economic challenges might also result in a lower prevalence. The possibility of as yet undefined genetic and environmental factors has also been suggested as a possible reason for the lower prevalence of PD in SSA [2].

It is difficult to draw much inference from, or to compare, hospital-based series in SSA because of the marked difference in methodology applied regarding diagnostic criteria, population characteristics, and the estimated proportion reported, as some studies did not discriminate between idiopathic PD and other causes of secondary Parkinsonism. Door-to-door surveys offer the best estimate of PD prevalence because they can detect as yet undiagnosed cases in the community among people with different health-seeking behaviors. However, a major challenge to this type of study is the high cost, which is inherently a major factor affecting research in SSA.

Care availability and accessibility

Even when PD patients are able to be diagnosed, treatment is often non-existent or irregular; monitoring is limited; multidisciplinary teams are rarely available; and patients often turn to local traditional healers for treatment [13]. The other challenge high-lighted is the paucity of neurologists and other health care personnel caring for PD patients. The situation is the same for neurosurgeons, neuroradiologists, geriatricians, PD nurses and other health care personnel. The treatment of patients after diagnosis is hampered by a lack of drugs, as these drugs are unavailable or unaffordable to the patients. Some of the available drugs are no longer used as first-line drug treatment in Europe and in other countries with a higher GDP and better-developed neurological services. For instance, anticholinergics and ergot DAs were used more than non-ergot DAs and MAO-B inhibitors in SSA. The impact of the high cost of PD treatment on access to PD drugs cannot be over-emphasized in a region where almost 50% of the population lives on less than 1.25 USD per day [52]. The location of the few health facilities being far away from patients' residences again increases the financial burden on the patient, as they have to pay for the cost of transportation and consultation out of pocket in a region where only a small minority have health insurance.

CONCLUSION

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This review has highlighted the challenges involved in conducting genetic and epidemiologic studies in SSA. It has also been shown that the currently available care for PD patients is grossly inadequate. Large-scale, state-of-the-art genetic and epidemiological studies will help to provide further insight into the role of genetic factors and other etiological factors such as toxin exposure in PD in SSA. Collaborative studies using the same methodology and staffed by personnel with comparable training will help establish a data set that could then be used to compare the PD prevalence rates across different populations. The establishment of minimal consensus management guidelines may help to improve the consistency and quality of care. International assistance is needed regarding improved public awareness of neurological diseases, training of health care workers, provision of affordable drugs and facilities for PD treatment and the monitoring of PD patients in the region.

Notes

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Conflicts of Interest

The authors have no financial conflicts of interest.

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