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Increasing Frequency of Parkinsonian Syndrome as a Reason for Admission to the Neurology Department of Befelatanana University Teaching Hospital, Madagascar

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Abstract

The number of parkinsonian syndrome patients in Africa is increasing. This study evaluated the increasing number of parkinsonian syndrome (PS) patients admitted to a hospital in Madagascar. A comparison was carried out between parkinsonism syndrome plus (PS+) and idiopathic Parkinson's Disease (PD) cases. Retrospectively, case records of patients with parkinsonism was reviewed between 2009 and 2018 in the Neurology Department of Befelatanana University Teaching Hospital, Antananarivo. Out of the 7343 patients seen in the unit over this period, 157 patients with PS were retained. It was found that PS frequency has increased significantly as a reason for admission since 2013. PS as a reason for admission rose from 0.64 % in 2009 to 29.30 % in 2018. The median age of diagnosis of PS was 60.75 years

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± 10.66. The mean age of disease onset was 57.95 years ± 10.99, with a mean diagnosis delay of 3.19 years and a sex ratio of 1.275. Among those with PS, 112 (71.33%) had PD and and 45 (28.66%) had other parkinsonian syndromes. It was also found that patients with PD had a longer diagnosis delay (p = 0.039), a higher Mini-Mental Status Examination (MMSE) scores (p = 0.035), and they were more dopa-sensitive (p = 0.007) than those with other parkinsonian syndromes. In the facility in Madagascar, the number of referrals for PS and PD has increased over time and they have the same features as parkinsonian syndromes in other African countries.

Keywords: Frequency, Antananarivo, Parkinsonian Syndrome, idiopathic Parkinson's disease

Introduction

Parkinsonian syndromes (PS) are neurological disorders sharing the characteristics of bradykinesia, akinesia, resting tremor, rigidity or hypertonia (Rajput, 1992). Parkinsonian syndromes are grouped into two major etiological classes: degenerative and non-degenerative. Degenerative PS includes idiopathic Parkinson's disease (IPD) and PS plus (degenerative parkinsonism other than idiopathic Parkinson's Disease). Non-degenerative PS has secondary induced causes (Ferrazzi et al., 2015). Parkinson's syndromes are, after dementia syndromes, the most frequent neurodegenerative disorders (Vidailhet, 2018). In sub-Saharan Africa, their prevalence and incidence have been lower based on a study in Nigeria (Akinymieni, 2012). In Madagascar, a study between 2014 and 2017 found parkinsonian syndromes to be an increasingly frequent reason for consultation in Neurology unit. Lack of public awareness of the disease and the lack of referrals to specialists have created gaps in the care of PS (Rasaholiarison et al., 2019). To evaluate the frequency of patients referred as PS and assess care gaps, the characteristics of patients referred to the center with parkinsonian syndromes was examined over a period of ten years. Also, a comparison was made between the frequency of other PS (parkinsonian syndrome plus and secondary parkinsonian syndrome) and idiopathic Parkinson's disease.

Methods

The study was carried out in the Neurology Department of the Joseph Raseta Befelatanana University Teaching Hospital, Antananarivo, which is a national referral center for neurological diseases in Madagascar. A descriptive and comparative retrospective single-center study was carried out over a ten-year period from 2009 to 2018. All inpatients diagnosed with parkinsonian

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syndrome seen in the Neurology Department of Befelatanana University Teaching Hospital were included, while patients with incomplete medical records were excluded in the study. It was hypothesized that there would be an annual increase in the number of patients with parkinsonism. This study examined the demographic and clinical characteristics, including age at diagnosis, duration of illness and sex (male, female), patient history (familial parkinsonism hypertension, diabetes, alcohol, or tobacco use), cognitive state as assessed by the Mini-Mental Status Examination (MMSE), presenting symptoms (neurological problem, tremor, gait disturbance, parkinsonian syndrome, stroke, rigidity, slowness, akinesia, others), existence of a typical parkinsonian syndrome (parkinsonian triad of bradykinesia, tremor, and rigidity without other signs) or parkinsonian syndrome plus on physical examination, dopa-sensitivity (dopa-sensitive, non-dopa-sensitive), and the initial treatment (dopaminergic agonists, anticholinergics, levodopa, other drugs). Finally, an assessment was done on the etiology of the PS, including idiopathic Parkinson's disease (IPD), parkinson syndrome plus (PS+) which are multiple system atrophy (MSA), progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), cortico-basal degeneration (CBD), and parkinsonism due to secondary causes. Demographic and clinical characteristics of IPD were compared to other parkinsonian syndromes.

Xlstat software was used for data processing and statistical testing. Results are shown as the absolute value, percent, and average depending on variable type. Continuous variables were reported as the median with extremes. Significant differences in the means of continuous variables were shown by the Student's t-test ($p < 0.05$). The frequency was calculated by the number of patients in each year by the total of inpatient retained. The MMSE (Mini-Mental Status Examination) was used to assess the cognitive status with a maximum score of 30/30. Scores below 24 are abnormal and compatible with a diagnosis of dementia. The dopa sensitivity of the patients was assessed by oral administration of 100 mg of immediate-acting levodopa. A positive response was defined as an improvement in symptoms and signs 30 minutes after administration.

Results

Parkinson syndrome (PS) was identified in 160 out of 7,343 patients hospitalized for neurological disorders (2.17%). Above those 160 included, 157 patients were retained after excluding three patients with incomplete data. A male predominance was noted 88/157 (56%) with a sex ratio of 1.275. It was found that the annual frequency of PS has increased markedly since 2013 except for that in 2015. The annual frequency ranged from 1/157 (0.6%) in

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2009 to 46/157 (29.3%) in 2018 (Figure 1). The mean age at onset of symptoms of PS was 57.95 ± 10.99 years. The median age at diagnosis of PS was 60.75 ± 10.66 years. The number of men with PS predominated over women (56.05%). Ninety-nine patients (63.06%) had no specific medical history, 43 (27.39%) were hypertensive, 3 (1.91%) were diabetics, 1 (0.64%) were both diabetic and hypertensive, 6 (3.82%) were alcoholic, and 5 (3.18%) had a history of familial parkinsonism time from onset of symptoms to the diagnosis of parkinsonism. The mean MMSE score for patients with Parkinson's disease was 28 (Table 1). The reasons for consultation and referral were tremor in 83 (52.86%) followed by slowness in 29 (18.47%), rigidity in 22 (14.01%), gait disorder in 18 (11.46 %), parkinsonian syndrome in 3 (1.91%), stroke in 1 (0.64%), and other neurological disorders in 1 (0.64%). Among those with parkinsonian syndromes, 112 patients (71.33%) had typical parkinsonian syndrome (PD), and 45 patients (28.66%) had other parkinsonian syndromes (either parkinson syndrome plus or secondary parkinsonism). It was found that 74% of the cases were dopa-sensitive. The treatment was levodopa in most cases (97 patients, 61.8%), followed by dopamine agonists for 46 patients (29.3%), anticholinergics for 7 patients (4.5%), and other drugs for 7 patients (4.5%). The main etiologies of parkinsonian syndromes were IPD in 112 patients (71.33%), MSA in 22 patients (14.01%), PSP in 2 patients (1.27%), CBD in 2 patients (1.27%), DLB in 5 patients (3.18%), and secondary parkinsonism in 14 patients (8.91%). In comparing IPD to other PS, it was found that patients with IPD had a longer delay in diagnosis (p = 0.039). Hence, they were more likely to have an unremarkable past medical history (p = 0.021), have a higher MMSE score (p = 0.035), and have a more marked dopa-sensitivity (p = 0.007) than other patients with PS (Table 1).

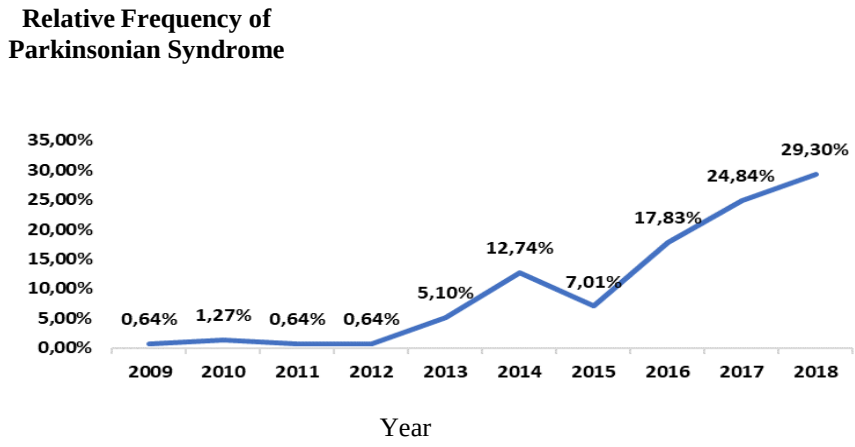

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Figure 1. Increasing frequency (number of patients with PS in a year/ total number of inpatients with PS) of the parkinsonian syndrome from 2009 to 2018 in the Neurology Department of Befelatanana University Teaching Hospital, Antananarivo

Table 1. Characteristics of parkinsonian syndromes (PS) seen in the Neurology Department of Befelatanana University Teaching Hospital, Antananarivo

Variables	Total	Idiopathic Parkinson's disease (PD) (N = 112)	Secondary and atypical parkinsonism (N = 45)	p
Age (years):				
At onset	57,95 [26 ; 80]	58,57 [23 ; 80]	56,42 [26 ; 83]	0,270
At diagnosis	60,75 [26 ; 83]	61,74 [32 ; 83]	58,24 [26 ; 83]	0,061
Diagnosis delay (years)	**3,19**	**3,43**	**2,5**	**0,039**
Gender :				
Male	88 (56,05%)	57 (50,94%)	31 (68,88%)	0,05
Female	69 (43,95%)	55 (49,10%)	14 (31,11%)	
Past history :				
Without particularity	99 (63,06%)	73 (65,17%)	26 (57,77%)	**0,021**
Familial PS*	5 (3,18%)	3 (2,67%)	2 (4,44%)	
MMSE**	28 [11 ; 30]	29 [20 ; 30]	27,68 [11 ; 30]	**0,035**
Dopamine sensitivity :				
Yes	116 (73,88%)	101 (90,17%)	15 (33,33%)	**0,007**
No	41 (26,11%)	11 (9,82%)	30 (66,66%)	

***PS:** Parkinsonian syndrome
****MMSE:** Mini-Mental Status Examination

Discussion

This is the first study in Madagascar to describe the frequency of parkinsonian syndrome in patients referred to a national center over a ten-year period. Number of patients with parkinsonism increases over time, and its main etiology is Parkinson's disease (PD). Referrals for Parkinson disease have increased due to the increasing of neurologists' number in Madagascar in recent years. However, some have become interested in movement disorders.

Some of the limitations of this study include being single-centered, concerned only inpatient, and retrospective. The study may not represent the nation as a whole or the outpatient population of patients. Due to the nature of the study, changes cannot be estimated in the incidence or prevalence of parkinsonian syndrome in Madagascar.

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During the study period, 160 patients out of 7,343 patients seen in the department were diagnosed with parkinsonian syndrome (2.17%). In the study of Okubadejo et al. (2010), the intra-hospital frequency of parkinsonism was 1.47%. El-Tallawy et al. (2013) found a regional prevalence of 0.31%. A higher frequency was found in this study because it was done at a neurological referral center. It was noted that the frequency of parkinsonian syndromes has increased since 2013 except in 2015. Few other studies have examined temporal trends in the frequency of parkinsonian syndromes. In this study, it is unlikely that it is due to increased incidence or prevalence but more likely due to increased patient awareness of potential for treatment of this disease and the increased number of care provider interests in PS and PD.

However, a study by Rocca et al. (2001) has shown a stable incidence of Parkinson's disease (1976-1990) in Olmstead, Minnesota. It appears that in this region of the northern United States, no new environmental risk factor for Parkinson's disease occurred during this period. The number of people with Parkinson's disease in Africa was estimated at 1.3 million patients in 2011, an increase compared to previous years. An increase in life expectancy has been observed in developing countries associated with an increase in age-related diseases such as Parkinson's disease and other parkinsonian syndromes (Cilia et al., 2011).

In this study, the mean age of onset of parkinsonian syndromes was 57.95 years ± 10.99, while the mean age of diagnosis of parkinsonian syndromes was 60.75 ± 10.66 years. In most patients, the onset of motor symptoms in PS is after age 40 (Kurland et al., 1969). Uitti et al. (1993), in a series of 934 PD patients, observed for over 22 years (1968-1990) a mean age at onset of 51.5 years. Feldman et al. (2011) reported a mean age at diagnosis of 75.5 ± 8.6 years with extremes between 43 and 94 years in a prospective cohort study based on the population of Swedish twins. Bushman et al. (2016) found an average age of diagnosis of 81.9 years (± 6.92). In another study, Darweesh et al. (2017) found a mean age of diagnosis of 65.3 years. These differences in age of onset compared to this study may reflect the youthfulness of the national population (INSTAT, 2012-2013).

In this study, men predominated over women (56.05%). According to the study by Hughes et al. (2002), over ten years, 89 were men (62.23%). Savica et al. (2017) reported a male preponderance with 279 men (60.5%). The protective role of estrogen may contribute to this sex difference in the incidence of Parkinson's disease (Rajput et al., 2003).

For the patients, 99 (63.06%) had no past medical history, 27.39% were hypertensive, 1.91% were diabetics, 3.82% alcohol-smoking, and 3.18% had a history of familial parkinsonism. Buschmann et al. (2016) reported on

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776 cases of parkinsonism with 52.1% being hypertensive, 14.2% were diabetic, 13.5% had a stroke, and 5.3% had a history of familial PD. The low rate of comorbidity in this series may be attributable to insufficient screening and investigation in the pre-hospital setting.

Hughes et al. (2002) described a diagnostic delay of 1.6 years (0-7 years). In addition, there was a diagnostic delay of 3.19 years in this study. In developed countries, the average time of diagnosis is around the first year of symptoms and no longer than the first two years after onset (Chrysostome et al., 2015). The longer delay in diagnosis in Madagascar can be explained by the few neurologists specializing in movement disorders.

The reasons for referral were tremor in 83 (52.86%) followed by slowness in 29 (18.47%), rigidity in 22 (14.01%), and walking disorders in 18 (11.46 %). According to Bostantjopoulou et al. (1991), tremor was the most frequent initial symptom observed in elderly subjects than in young subjects with IPD. Thus, this was the most numerous in the study. In the literature, the cardinal signs of parkinsonian syndrome are often present in IPD but variable in MSA, PSP, CBD, and drug-induced parkinsonism (Alvarez et al., 2007). Compared to patients with PS, 71.33% had IPD and 28.66% had other PS. There was a male predominance in both idiopathic Parkinson's disease (50.89%) and other parkinsonian syndromes (68.88%). In the study by Okobadejo et al. (2010), the intra-hospital frequency was 79% for Parkinson's disease and 21% for secondary parkinsonism predominance. In a regional study of Kano, Femi et al. (2012) found the frequency of IPD was 83.3% and 16.7% for secondary parkinsonism with a male predominance of 63.5% in IPD and 13.5% for secondary parkinsonism.

The levodopa test was positive in 116 patients (74%). This majority of dopa-sensitivity is explained by the high incidence of IPD, which is dopa-sensitive in most cases. IPD is sensitive to dopa in 70 to over 80% of cases (Wenning et al., 2000; Tolosa et al., 1975; Winikates et al., 1999). Since 74% of the cases were dopa-sensitive, treatment with levodopa was undertaken in most cases (97 patients, 61.8%), followed by dopamine agonists for 46 patients (29.3%), anticholinergics for 7 patients (4.5%), and other drugs for 7 patients (4.5%). Holden et al. (2019) studied 24 parkinsonian patients and 37.5% were on MAO-B inhibitors, 16.7% on amantadine, 16.7% on donepezil, and 4.2% on trihexyphenidyl. Levodopa remains the first-line recommendation in the symptomatic treatment of parkinsonian syndromes. Etiological treatments for neurodegenerative diseases are being developed and tested. Molecular diagnosis and treatment are emerging and will require the cooperation of primary care physicians with specialized centers (Levin et al., 2016). The main etiologies of parkinsonian syndromes were IPD in 112

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patients (71.3%), MSA in 22 (14.0%), PSP in 2 patients (1.3%), CBD in 2 patients (1.27%), DLB in 5 patients (3.2%), and secondary parkinsonism in 4 patients (8.9%). El-Tallawy et al. (2013) found that 33.6% of patients had secondary parkinsonism, including 28.6% of vascular origin. Secondary parkinsonism accounts for 0.5% of Black patients and 1.15% of Whites. The incidence in Africa of Parkinson's syndrome has been increasing as the population has increased in age (Van Den Eeden et al., 2003).

Conclusion

Parkinsonian syndromes are not rare in Madagascar but may be underdiagnosed. As in other African countries, the number affected has increased. It is due to increased patient awareness of potential for treatment of this disease and increased number of neurologists. As in other African countries, a delay in diagnosis is common. The dominant etiology is idiopathic Parkinson's disease. In a country like Madagascar, establishing adequate clinical facilities for the diagnosis of parkinsonian syndromes is necessary. Thus, it is implementing a circuit of care with other disciplines (physical rehabilitation) for treatment. Parkinsonian syndromes constitute a diagnostic and treatment burden for Madagascar. A larger study on the national incidence and prevalence (inpatient and outpatient) of Parkinson's disease and other parkinsonian syndromes is needed.

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