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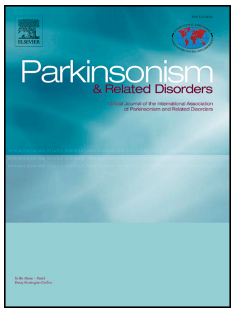

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Prevalence of pain in patients with Parkinson`s disease in Addis Ababa, Ethiopia

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ABSTRACT

Introduction: Pain is a common non-motor feature encountered by patients with Parkinson's disease. Recognition and accurate characterization of pain is crucial for the optimal treatment of Parkinson's disease patients. Pain has been associated with poverty and ethnicity. We determined the prevalence of pain in Parkinson's disease patients in Ethiopia.

Method: We conducted a cross-sectional study for a six month period from April 01, 2017 – September 30, 2017 with patients with Parkinson's disease who were attending two neurology referral clinics in Addis Ababa, Ethiopia to assess for the prevalence and the characterization of pain.

Results: We surveyed 103 patients with Parkinson's disease. Of these, 87/103 (84%) had symptoms of pain. Only 16/87 (18.4%) received pain medications, and no one was referred for physiotherapy.

Conclusion: In Ethiopia, the prevalence of pain in Parkinson`s disease patients is amongst the highest in the world, under recognized and undertreated.

INTRODUCTION

The cardinal features of Parkinson's disease (PD) include resting tremor, rigidity, bradykinesia and postural instability. However, patients also experience non-motor symptoms (NMS) including autonomic disturbances, sleep problems, pain, paresthesias and cognitive impairment.[1]

The reported prevalence of pain in PD varies between 40% to 85%.[2-7]Pain adversely affects quality of life.[8]An international multicenter study showed that pain is amongst the most common non-motor symptoms (NMS) during early morning off periods.[9]

A recent study from Germany showed a correlation between chronic pain and poverty.[10] An additional study from the United States showed that older adults in poverty, and African American men, were more likely to report that pain interfered with their daily work.[11] All reports on pain in PD have been from either North America or Europe.[2-7] The prevalence of pain in those with PD from impoverished nations has not been reported to our knowledge.

Ethiopia is among the countries with the largest population in Africa estimated to be 96,633,458 in 2014. The life expectancy is 58.4 years for men and 63.2 years for women. Ethiopia is in the lowest 10% of GDP per capita.[12] The prevalence of PD in Ethiopia was 7/100,000 in a community-based study in 1986 – 1988.[13] However, the prevalence is expected to increase dramatically in the next several decades as life expectancy increases.[1]

To determine if those with PD in Ethiopia experienced pain similar to other populations, we studied the prevalence of pain in all patients presenting with PD to two outpatient clinics in Ethiopia.

METHODS

Addis Ababa University School of Medicine (AAU) started Ethiopia's first neurology residency program in 2006. The vast majority of the patients with PD at AAU are seen at either the Zewditu Memorial hospital or Tikur Anbessa Specialized hospital. We invited all patients with PD presenting to these institutions from April 1, 2017- September 30, 2017 to participate in this cross-sectional study.

Patients were enrolled in the study if they fulfilled the UK Parkinson's Disease Society Brain Bank criteria and consented to enroll.

We translated the King's Parkinson's disease Pain Scale (KPP) into Amharic.[14] This scale is an internationally validated scale to measure different types of pain in patients with PD. The scale consists of seven main domains divided into 14 items. Each item rates a severity score from 0-3, and a frequency score from 0-4. An item's sub-score is the product of severity times frequency. The total score is the sum of the sub-scores, resulting in a possible total score of 0- 168.[14]

We used the Patient Health Questionairre-9 (PHQ-9), translated into Amharic, to assess depression. This has been validated locally in Ethiopia.[15] The PHQ-9 is a short hand tool used to screen, diagnose and monitor depression and its severity. The score of the PHQ-9 is interpreted as: 5-9 minimal symptoms; 10-14 minor depression; 15-19 major depression (moderate); $\geq$ 20 major depression (severe).

Data was collected by staff neurologists, the principal investigator or senior neurology residents. Demographic and clinical characteristics were presented as frequencies and means ± standard deviation (SD).

We categorized those who had pain into those who had at least one severe pain vs. those who had no severe pain. We then performed a cross-tabulation of variables and binary logistic regression analysis assessing age, gender, duration of symptoms, duration of treatment, PD stage, and presence of depression with the presence of severe pain. We showed the strength of association with p value, adjusted odds ratio, and 95% confidence interval. Statistical result with a value $p < 0.05$ was considered significant. The data was analyzed using SPSS (Version 20).

The research proposal was approved by the Ethical Review Committee of the Department of Neurology, School of Medicine Addis Ababa University. Each study participant consented to participate in the study.

RESULTS

One hundred and three patients (65 men; 38 women) were recruited consecutively into the study. No patient refused consenting into the study. The median age was 64 years (IQR= 57-72). All patients were receiving either levodopa (plus dopa-decarboxylase inhibitor) and/or trihexyphenidyl for at least three months during the interview except one patient who was newly diagnosed. The demographics of the patients are shown in Table 1.

Table 2 shows our results on the experience of pain in our patients. In this study 87/103 (84%) of patients had some sort of pain, with musculoskeletal pain being the most common, followed by pain related to turning in bed at night, visceral pain and off-dystonia. According to the median sub-scores, musculoskeletal pain, central pain, pain related to difficulty turning in bed, radicular pain and burning limb pain were the most bothersome.

The range of the Total KPP scale score was 0–72, out of a possible 168. The median KPP score was 14 (IQR 4-27).

Of the 103 patients, 41 (39.8%) had depressive symptoms. The severity of the depression was mild in 23 (22.3%), moderate in 12 (11.7%) and severe in 6 (5.8%). Only 13/41 (31.7%) patients with depression were receiving anti-depressant medication.

Of age, gender, duration of symptoms, duration of treatment, PD stage, and presence of depression, the only statistically significant association with severe pain (defined as a severity score of three on any KPP item) was depression. 61.1% of patients with symptoms of depression

had at least 1 severe pain; whereas 74.2% of cases with minimal symptoms of depression had no severe pain at all. ($p<0.001$, AOR = 4, and 95% CI 1.4 -11)

Despite the high incidence of pain in the patients, only 16/103 (15.5%) were receiving pain management, predominantly NSAIDs (diclofenac/indomethacin) and amitriptyline. None were prescribed physiotherapy, but 21/103 (20.4%) were doing exercises at home.

DISCUSSION

In the context of international human rights law, every patient has the right to be free of pain.[16] The majority of patients managed in medical and surgical wards in Ethiopia receive below the standard care of pain assessment and management.[17-18] Therefore, recognition and treatment of pain is crucial.[19] However, pain in PD patients may not be obvious to detect. Physicians frequently prioritize the cardinal disease features over distressing pain.[20] In fact, patients with PD report an average pain level greater than the general population, with >50% of patients reporting one, 24% reporting two and 5% reporting three pain types.[1]

Our study showed that the prevalence of pain in PD patients in our outpatient clinics is exceedingly high. 84% of our patients reported pain. The most common pain in our population was musculoskeletal pain followed by pain related to difficulty turning in the bed at night. Both of these were also amongst the most bothersome according to their sub-scores.

The prevalence of pain varies from study to study. The prevalence of pain in our population is similar to that reported in the United Kingdom (85%)[3], and in Norway (83%)[7]. Other studies however have reported pain at lower prevalence: 46% in Chicago[2], 40-69.9% in Italy[4-5], and 61.7% in France[5]. Ethiopian PD patients therefore experience pain at one of the highest rates in the world. Determining whether poverty explains this finding requires further study.

99.0% of our patients were on treatment at the time of their evaluation, with 46.0% on trihexyphenidyl. We could not calculate the levodopa equivalent daily dose (LEDD) as there is no known levodopa equivalent dose for trihexyphenidyl.[21] Those authors explain that this is due

to the "…poor effect on akinesia, and their low usage in modern practice." Although anticholinergics may be rarely used to treat PD in the West, we found that trihexyphenidyl is used in close to half of Ethiopian patients with PD. We suspect this is due to the low cost.

A similar study in the Slovak Republic showed that 76% of patients with PD had pain, in which 41% had musculoskeletal pain. They also compared the presence of pain and severity of depression. Those experiencing any type of pain showed significantly a higher score of BDI (16.6± 9.4 vs. 9.7 ±7.6; P value <0.001), and PDQ-8 (10.1 ± 5.3 vs. 7.0 ± 6.4; p value = 0.02).[22]

Other authors report that musculoskeletal pain is the most frequent pain (48%), followed by pain related to dystonia (26%). Similarly, patients with PD who had pain experienced more depressive symptoms.[23]

We found that the most frequent pain described was musculoskeletal. This can sometimes result from immobility due to rigidity and akinesia. In one retrospective study, 33% of the PD patients were initially diagnosed as having degenerative spinal disease, osteoarthritis and frozen shoulder. The average time from first symptom to dopaminergic therapy was 6.6 years in those presenting with musculoskeletal pain, but 2.3 years in those with classic PD features.[24]

The prevalence of nocturnal pain was high in our study. These patients had restless leg syndrome (31.1%) and pain related to difficulty turning in bed at night (45.4%). Both of these could potentially be ameliorated by proper dopaminergic treatment.

A high percentage of our patients reported experiencing visceral pain, defined by the question "Do you experience pain related to an internal organ (e.g. liver, stomach or bowels)?" The only available formulation of levodopa in Ethiopia is the 25/250 tablet. Carbidopa alone preparation is not available, nor is the 25/100 formulation. A lower carbidopa: levodopa ratio may result in higher GI discomfort, and may explain some of these patient's complaints.

In our patients, central pain was relatively common and severe. In other studies it was estimated to be present in 10-12% of PD patients.[25] The central pain pathway in PD is complex, and may involve cortical and subcortical sensory structures in the basal ganglia and the thalamocortical-basal ganglia circuits.

Off-period dystonia pain was also common. Dystonic spasms frequently affect the toes or feet.[26] This too could potentially be addressed by optimizing dopaminergic treatment.

Radicular pain was not frequent in our population but when present was very bothersome. Radicular pain accounted for 14% of the pain syndromes experienced by patients with PD in one survey.[3] Because PD patients often develop postural abnormalities and dystonia, intervertebral disc changes compressing the nerve roots can result.[25]

Pain and depression are comorbid and non-motor symptoms of PD. As a matter of fact, the underlying mechanisms of pain and depression overlap and both symptoms involve abnormalities of noradrenalin and serotonin.[23] We examined the correlation between pain and other variables. Of these, depression was significantly associated with severity of pain in PD patients.

Although 59% of patients with pain had reported their pain symptoms to their physician, only 15.5% were receiving pain management. Only 31.7% of those with depression were on treatment. Because patients may not report their pain or depressive symptoms spontaneously, physicians must actively explore these two areas with them.

Our study had limitations. It was not population-based- rather it was performed in only two outpatient clinics in the capital city. Furthermore, because of the poor educational status of many of the patients, they often struggled to adequately explain their pain, which may have led to misclassification.

On the other hand, this study was performed in the only teaching hospital in Ethiopia training neurologists. In Ethiopia, there are approximately 36 neurologists in the entire country. The vast majority are in Addis Ababa. Clearly, most patients with PD in Ethiopia are being treated by non-neurologists, non-physicians or not at all. This problem is shared across sub Saharan Africa.[27] We suspect that the care of most patients with PD in sub Saharan Africa is even less comprehensive than in our two clinics. Better education of general physicians and nurses on the importance of screening for pain and depression in these patients is paramount.

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AUTHORS' ROLES

Dr Hirsi	Conception and Design, acquisition of data, analysis and interpretation of data Drafting the article and critical revision Final approval of submitted version
Dr. Yifru	Conception and Design, analysis and interpretation of data Critical revision Final approval of submitted version
Dr. Metaferia	Conception and Design, analysis and interpretation of data Critical revision Final approval of submitted version
Dr. Bower	Conception and Design, analysis and interpretation of data Critical revision Final approval of submitted version

DECLARATION OF INTEREST

Dr. Hirsi: None
Dr. Yifru: None
Dr. Metaferia: None
Dr. Bower: None

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Table.1
Sociodemographic characteristics of PD patients in the study

Variable	Category	Frequency	Percent
Sex	Female	38	36.9%
	Male	65	63.1%
Age group	<50	6	5.8%
	50-64	46	44.7%
	>64	51	49.5%
Marital status	Single	7	6.8%
	Married	65	63.1%
	Living together	2	1.9%
	Widowed	20	19.4%
	Separated	9	8.7%
Education	Can't read or write	39	37.9%
	Elementary	26	25.2%
	High school	14	13.6%
	Tertiary	24	23.3%
Duration of PD symptoms	≤ 5	57	55.3%
	6-10	32	31.1%
	>10	14	13.6%
Duration of treatment	≤ 5	73	70.9%
	6-10	21	20.4%
	>10	9	8.7%
Type of medicine	Levodopa only	54	52.4%
	Trihexyphenidyl only	6	5.82%
	Combination	42	40.78
	No therapy	1	1.0%
Hoehn and Yahr scale	Stage 1	32	31.1%
	Stage 2	41	39.8%
	Stage 3	20	19.4%
	Stage 4	6	5.8%
	Stage 5	4	3.9%

Table 2
Distribution frequency of pain in PD patients at TASH and ZMH OPD neurology clinics

Specific type of pain	No. of patients with specific pain	severity		Frequency		Median Subscore (IQR 25%-75%)
		Score	No. of patients (Percent)	Score	No. of patients (Percent)	
I. Musculoskeletal pain						
1.Pain around the joints	70/103(68%)	1	30/103(29.1%)	1	18/103(17.5%)	4 (IQR 2-6)
		2	27/103(26.2%)	2	26/103(25.2%)	
		3	13/103(12.6%)	3	8/103(7.8%)	
				4	18/103(17.5%)	
II. Chronic pain						
2. Central pain	33/103(32%)	1	14/103(13.6%)	1	6/103(5.8%)	4 (IQR 2-6)
		2	16/103(15.5%)	2	17/103(16.5%)	
		3	3/103(2.9%)	3	6/103(5.8%)	
				4	4/103(3.9%)	
3. visceral pain	45/103(43.9%)	1	23/103(22.3%)	1	15/103(14.6%)	2 (IQR 1.5-6)
		2	13/103(12.6%)	2	16/103(15.5%)	
		3	9/103(8.7%)	3	6/103(5.8%)	
				4	8/103(7.8%)	
III. Fluctuation-related pain						
4.Dyskinetic pain	34/104(33%)	1	19/103(18.4%)	1	11/103(10.7%)	2 (IQR 1-4)
		2	13/103(12.6%)	2	16/103(15.5%)	
		3	2/103(1.9%)	3	4/103(3. 9%)	
				4	3/103(2.9%)	
5.“Off” period dystonia	37/103 (36%)	1	19/103(18.4%)	1	9/103(8.7%)	3 (IQR 2-4)
		2	14/103(13.6%)	2	16/103(15.5%)	
		3	4/103(3.9%)	3	8/103(7.8%)	
				4	4/103(3.9%)	
6.Off” period pain	30/103 (29%)	1	15/103(14.6%)	1	10/103(9.7%)	2 (IQR1-5.5)
		2	10/103(9.7%)	2	11/103(10.7%)	
		3	5/103(4.9%)	3	3/103(2.9%)	
				4	6/103(5.8%)	
IV. Nocturnal pain						
7.Restless leg syndrome	32/103(31%)	1	21/103(20.4%)	1	12/103(11.7%)	2 (IQR 1-4)
		2	8/103(7.8%)	2	12/103(11.7%)	
		3	3/103(2.9%)	3	3/103(2.9%)	
				4	5/103(4.9%)	
8.Pain related to difficulty turning in bed at night	47/103(45.6%)	1	13/103(12.6%)	1	9/103(8.7%)	4 (IQR 2-9)
		2	19/103(18.4%)	2	16/103(15.5%)	
		3	15/103(14.6%)	3	7/103(6.8%)	

				4	15/103(14.6%)	
V. Oro-facial pain						
9.Pain when chewing	8/103(7.7%)	1	7/103(6.8%)	1	4/103(3.9%)	1 (IQR 1-4)
		2	1/103(1.0%)	2	1/103(1.0%)	
		3	0	3	0	
				4	3/103(2.9%)	
10.Grinding their teeth during night	20/103(19.4%)	1	12/103(11.7%)	1	83/103(80.6%)	2 (IQR 1-3)
		2	7/103(6.8%)	2	9/103(8.7%)	
		3	1/103(1.0%)	3	10/103(9.7%)	
				4	1/103(1.0%)	
11.Burning mouth syndrome	4/104(3.9%)	1	3/103(2.9%)	1	2/103(1.9%)	1 (IQR 1-2.5)
		2	1/103(1%)	2	2/103(1.9%)	
		3	0	3	0	
				4	0	
VI. Discoloration; edema/swelling						
12.Burning pain in limbs	37/103(35.9%)	1	15/103(14.6%)	1	8/103(7.8%)	4 (IQR 2-5.5)
		2	17/103(16.5%)	2	19/103(18.4%)	
		3	5/103(4.9%)	3	4/103(3.9%)	
				4	6/103(5.8%)	
13.Generalized lower abdominal pain	22/103(21.3%)	1	12/103(11.7%)	1	10/103(9.7%)	2 (IQR 1-4)
		2	8/103(7.8%)	2	8/103(7.8%)	
		3	2/103(1.9%)	3	3/103(2.9%)	
				4	1/103(1.0%)	
VII. **Radicular pain**						
14. Shooting pain/pin & needles down the limbs	27/103(26.2%)	1	8/103(7.8%)	1	4/103(3.9%)	4 (IQR 2-6)
		2	13/103(12.6%)	2	14/103(13.6%)	
		3	6/103(5.8%)	3	3/103(2.9%)	
				4	6/103(5.8%)	

Key: **KPP scale score:**

Severity:

0 = None,
1 = Mild (symptoms present but causes little distress or disturbance to patient)
2 = Moderate (some distress or disturbance to patient)
3 = Severe (major source of distress or disturbance to patient)

Frequency:

0 = Never
1= Rarely (<1/wk)
2= Often (1/wk)
3 = Frequent (several times per week)
4 = Very frequent (daily or all the time)

HIGHLIGHTS

- This is the first report of pain in patients with Parkinson's disease living in sub Saharan Africa
- 84% of patients with Parkinson's disease reported pain
- Some of the pain the patients experienced could be ameliorated by optimization of dopaminergic therapy
- The presence of depression was significantly associated with severe pain.