White Matter Hyperintensity in Parkinson's Disease Patients in Addis Ababa, Ethiopia

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Research Article

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Abstract

Background: The clinical significance of white matter hyperintensity (WMH) on brain magnetic resonance image (MRI) in Parkinson's disease (PD) patients was not sufficiently understood. Little is known about WMH in PD patients in sub Saharan Africa (SSA). The objectives of this study were to determine white matter hyperintensity and associated factors in Ethiopian PD patients.

Method: A cross-sectional observational study was conducted in 42 PD patients with WMH and 42 PD patients with normal MRI in Addis Ababa, Ethiopia. Both descriptive and analytical statistics were used to analyze the data.

Results: Total of 84 patients with PD was included in the analysis. The overall mean age was 61.5 (11.6) years. Young onset PD (≤ 50 years) accounted 16.7%. Males accounted 67.9%. Tremor dominant PD accounted 88.1%. Forgetfulness and hallucination was reported by 8.3% and 13.1% respectively. The median serum vitamin D and the mean hemoglobin level was 14.9 (8.3 – 20.2) ng/mL and 14.8 (13.8) g/L respectively. Hypovitaminosis D was observed in 40.5% of PD patients; similarly, anemia was observed in 27.4%. Negative correlation was observed between participant's age and their respective hemoglobin level. The prevalence of hypertension, diabetes, and dyslipidemia was 29.8%, 13.1%, and 20.2% respectively. No association was observed between white matter hyperintensity and young onset PD, hypovitaminosis D, hypertension, and diabetes. Age and dyslipidemia were found to be independent predictor of white matter hyperintensity, when adjusted for the covariates.

Conclusion: The present study indicates advanced age and dyslipidemia were associated with increased risk of having white matter hyperintensity on brain MRI of Ethiopian PD patients compared to those patients with normal MRI. Even though non-significant, the trend of vascular risk factors was in line with WMH.

1. Introduction

The global burden of Parkinson's disease has more than doubled since the past several decades; as a result of increasing numbers of older people, with potential contributions from longer disease duration and environmental factors. Demographic and potentially other factors are poised to increase the future burden of Parkinson's disease substantially, especially in developing countries such as sub Saharan Africa (SSA) (1, 2). According to the community-based survey of neurological disorders in rural central Ethiopia, the prevalence of PD is 7/100,000 (3).

In the last few decades due to significant improvement in accessing advanced imaging tests such as magnetic resonance images (MRI); increasing evidences have been obtain on the burden of white matter hyperintensity (WMH) in Parkinson's disease patients (4). There are two types of white matter hyperintensity; the first is periventricular hyperintensity (PVH). The second type is deep hyperintensity (DH) (5). White matter hyperintensity can be diagnosed both by brain MRI and computerized tomography

(CT); however, MRI is more sensitive (6). Therefore, quantification of WMH can be done visually using different assessment scales such as Scheltens scale (6–8).

The clinical significance of this WMH in PD patients was not sufficiently understood. However, there are scientific evidences associating the presence of WMH in PD patients with advanced age; cognitive decline; gait, mood; urinary continence; advanced disease stages; and disease severity (4, 9–11). A case control study by Piccini et al. 1995 (5), showed the frequency and the extent of periventricular hyperintensity was significantly higher in patients with PD than in healthy subjects. Moreover, within the periventricular hyperintensity had significantly shorter disease duration and PD group, the patients who had greater disease severity. There are accumulating scientific evidences supporting possible association between hypovitaminosis D and burden of WMH, especially in elderly individuals (12). According to study done by Prager et al. 2014 (12), a significant negative association was observed between low vitamin D and the number of confluent juxtacortical white matter T2 hyperintensity. Currently, major paucity of scientific evidences was observed in sub Saharan Africa regarding the clinical correlation and significance of white matter hyperintensity among African PD patients. Therefore, the objectives of this study were to determine white matter hyperintensity and associated factors in Ethiopian PD patients.

2. Materials And Methods

2.1. Study objective and study setting

The study was conducted at the outpatient neurology clinics of Yehuleshet Specialty Clinic (YSC) in Addis Ababa, Ethiopia. Yehuleshet Specialty Clinic is a specialty clinic located at the heart of Addis Ababa. The clinic is equipped with 0.35 tesla magnetic resonance image (MRI) machine, 4 latest 32-channel Nicolet video electroencephalography (EEG) machines, 4 latest nerve conduction study (NCS)/electromyography (EMG) machines, and seven EEG-trained nurses.

2.2. Study period and design

A cross-sectional observational study was conducted between May 2020 and February 2021. Total of 84 PD (42 patients with confirmed PD with white matter hyperintensity and 42 PD patients with normal brain MRI) were included in the analysis.

2.3. Data collection tool and procedure

A structured questionnaire was used in assessing the demography and clinical characteristics of PD patients. All the patients were clinically evaluated and questionnaires were administered. All patients were evaluated and diagnosed using UK Parkinson's Disease Society Brain Bank (UKBB) by board certified neurologists. Additional data clinical were extracted from individual patient’s medical recorder data.

2.4. MRI data acquisition and white matter hyperintensity scoring

All the 84 brain MRI results were reviewed by a certified neuroradiologist. Out of the 84 brain MRIs, half were labeled as MRI with white matter hyperintensity. Those MRIs with white matter hyperintensity were further scored as a periventricular hyperintensity and deep hyperintensity using the modified Scheltens scale (6–8). Detailed description of the WMH scoring of the 42 PD patients will be part of the follow up manuscript.

2.5. Data analysis

Variables were described using means, median, frequency, percentile, and standard deviation, and interquartile range. Associations were done using chi square or Fisher exact test, logistic regression analysis and results were presented using odds ratio (OR), and p value was set at < 0.05 as statistically significant.

2.6. Ethical considerations:

The study received ethical approval from City Government of Addis Ababa Health Bureau Ethical Clearance Committee (Protocol number: A/A/HB/3510/227). All subjects provided written and verbal consent before conducting the interview. All the methods in the present study were performed in accordance with the relevant guidelines and regulations.

3. Results

3.1. Baseline characteristics of study participants

In the present study, we have enrolled 42 PD patients having normal brain MRI with 42 PD patients who have a white matter hyperintensity (WMH) on their MRI. Overall, the mean age was 61.5 (11.6) years. Young onset PD (≤ 50 years) accounted 16.7%. Males accounted for nearly two-third of the study participants (n = 57, 67.9%). The median duration of months was 12 (6–36) months. Tremor dominant PD accounted for the majority (88.1%); more than of the participants were H & Y stage 1 and 2; and majority of the patients were on levodopa treatment (85.7%). Forgetfulness and hallucination was reported by 8.3% and 13.1% respectively. The median serum vitamin D and the median hemoglobin level was 14.9 (8.3–20.2) ng/mL and 14.8 (13.8) g/L respectively. Hypovitaminosis D was observed in 40.5% of PD patients; similarly, anemia was observed in 27.4%. Negative correlation was observed between participant's age and their respective hemoglobin level ($p = 0.002$) (Fig. 1). The prevalence of cardiometabolic risk factors such as hypertension, diabetes, and dyslipidemia was 29.8%, 13.1%, and 20.2% respectively (Table 1).

Table 1
Baseline characteristics of study participants (n = 84)

Characteristics	Values
Age in years (mean, 1SD)	61.5 (11.6)
Young onset PD (n, %)	14 (16.7)
Male (n, %)	57 (67.9)
Types of PD (n, %)	
Tremor dominant	74 (88.1)
Akinetic rigidity dominant	6 (7.1)
Postural/Gait Dominant	1 (1.2)
Duration of illness in months (median, IQR)	12 (6–36)
HY stage 1 & 2 (n, %)	46 (54.8)
Vitamin D level (median, IQR)	14.9 (8.3–20.2)
Hemoglobin level (mean, 1SD)	14.8 (13.8)
Levodopa treatment (n, %)	72 (85.7)
Anticholinergic treatment (n, %)	20 (23.8)
Forgetfulness (n, %)	7 (8.3)
Hallucination (n, %)	11 (13.1)
Hypertension (n, %)	25 (29.8)
Diabetes mellitus (n, %)	11 (13.1)
Dyslipidemia (n, %)	17 (20.2)
Normal MRI (n, %)	42 (50)
White and deep matter hyperintensity (n, %)	42 (50)

3.2. Comparison of white matter hyperintensity group with normal MRI group

In the present survey, we compared the 42 PD patients with normal MRI with equal number of PD patients with white matter hyperintensity to identify risk factors for WMH. Significant proportion of young onset PD patients had normal brain MRI than WMH (p = 0.03). The mean age of participants with WMH was significantly higher than patients with normal brain MRI (p = 0.001) (Fig. 2). No difference was observed between the two groups regarding, gender; types of PD; and PD disease stage (Table 2). In the present study, vitamin D deficiency was not associated with white matter hyperintensity on brain MRI (p = 0.42).

Even though statistically non-significant, higher proportion of individuals on levodopa treatment (p = 0.21); patients who reported forgetfulness (p = 0.22); and hallucination (p = 0.11) were found to have WMH compared to those without these symptoms. Among the cardiometabolic risk factors, dyslipidemia showed near-significant association with WMH on brain MRI of PD patients (p = 0.05). In addition, even though non-significant, hypertension (p = 0.23) and diabetes (p = 0.33) showed positive trends with WMH on brain MRI (Table 2).

Table 2
Risk factors of white matter hyperintensity in study participants (n = 84)

Characteristics	Brain MRI findings		p value
	Normal N = 42	White matter hyperintensity N = 42	
Young onset PD (n, %)	11 (13.1)	3 (3.6)	0.03
Male (n, %)	27 (32.1)	30 (35.7)	0.48
Female (n, %)	15 (17.9)	12 (14.3)	
Types of PD (n, %)			
Tremor dominant	37 (45.7)	37 (45.7)	0.71
Non-tremor dominant	3 (3.7)	3 (3.7)	
Hoehn and Yahr (HY) stage (n, %)			
HY stage 1 & 2	22 (26.2)	24 (28.6)	0.66
HY stage 3 & 4	20 (23.8)	18 (21.4)	
Vitamin D deficiency (n, %)			
Yes	20 (51.3)	14 (35.9)	0.42
No	2 (5.1)	3 (7.7)	
Anemia (n, %)			
Yes	15 (19.5)	8 (10.4)	0.09
No	24 (31.2)	30 (39)	
Levodopa treatment (n, %)			
Yes	34 (40.5)	38 (45.2)	0.21
No	8 (9.5)	4 (4.8)	
Anticholinergic treatment (n, %)			
Yes	10 (11.9)	10 (11.9)	0.98
No	32 (38.1)	32 (38.1)	
Forgetfulness (n, %)			
Yes	2 (2.4)	5 (6)	0.22
No	40 (48.2)	36 (43.4)	
Hallucination (n, %)			

Characteristics	Brain MRI findings		p value
	Normal N = 42	White matter hyperintensity N = 42	
Yes	3 (3.6)	8 (9.5)	0.11
No	39 (46.4)	34 (40.5)	
Hypertension (n, %)			
Yes	10 (11.9)	15 (17.9)	0.23
No	32 (38.1)	27 (32.1)	
Diabetes mellitus (n, %)			
Yes	4 (4.8)	7 (8.3)	0.33
No	38 (45.2)	35 (41.7)	
Dyslipidemia (n, %)			
Yes	5 (6)	12 (14.3)	0.05
No	37 (44)	30 (35.7)	

3.3. Logistic regression analysis for white matter hyperintensity and covariates

In the present study, in both univariate and multivariate logistic regression analysis, age of the patients was found to be independent predictor of white matter hyperintensity; when adjusted for gender, levodopa treatment, forgetfulness, and dyslipidemia (AOR 1.08, 95% CI 1.03–1.14, p = 0.002). Similarly, even though no association was observed in univariate analysis; significant association was observed between the presences of dyslipidemia and white matter hyperintensity in our PD patients when adjusted for the other covariates (AOR 4.23, 95% CI 1.08–16.51, p = 0.03) (Table 3).

Table 3
Logistics regression analysis of white matter hyperintensity and covariates (n = 84)

Characteristics	COR	95% CI	P value	AOR	95% CI	P value
Age in years	1.07	1.03–1.12	0.003	1.08	1.03–1.14	0.002
Gender						
Female	Ref.					
Male	0.72	0.29–1.81	0.48	0.57	0.19–1.74	0.33
Levodopa treatment						
No	Ref.					
Yes	2.24	0.62–8.09	0.22	2.89	0.69–12.05	0.15
Forgetfulness						
No	Ref.					
Yes	2.78	0.51–15.21	0.24	1.56	0.25–9.70	0.64
Dyslipidemia						
No	Ref.					
Yes	2.96	0.94–9.34	0.06	4.23	1.08–16.51	0.03
¶COR: Crude odds ratio; AOR: Adjusted odds ratio; CI: Confidence interval						

4. Discussion And Conclusion

To our knowledge this is the first study to report white matter hyperintensity and predictors in PD patients in Ethiopia. The mean age of study participants was comparable to previous reports from Ethiopia (13, 14). Majorities of the participants were males; were on levodopa; and tremor dominant. Hypovitaminosis D was observed in close to half of the study participants. Anemia was observed in nearly one third of participants. Furthermore, negative correlation was observed increasing age and anemia. Age and dyslipidemia were found to be independent predictor of white matter hyperintensity.

In the present study, young age was associated with lower risk of WMH on brain MRI. This finding is in congruent with previous reported studied (8, 9). Likewise, age was independent predictor of WMH. This is likely because of the fact that, white matter hyperintensity is common among elderly individuals compared to younger age group. Furthermore, cardiometabolic risk factors that often associated with WMH such as hypertension, diabetes, and dyslipidemia were less prevalent in young age PD patients compared to the older age patients (Table 2). Thus, it's important to screen older patients with PD for WMH. In current observation, no association was found between disease stage and types of PD. These findings were contrary to previously reported studies; which reported WMH among PD patients with

advanced disease stage and tremor dominant PD variants (5, 15, 16). These discrepancies could be explained by the fact that majorities of our PD patients had mild to moderate disease stage.

In the present study, even though non-significant, the prevalence of modifiable vascular risk factors such as hypertension and diabetes mellitus was higher in PD with MRI evidences of WMH compared to those individuals with normal MRI. However, significant proportions of PD patients with dyslipidemia have WMH compared to individuals with no-dyslipidemia; and dyslipidemia was independent predictor of WMH. These findings were in line with similar report by Chahine et al. 2019 (17), which indicates, modifiable vascular risk factors are associated with white matter hyper intensities on brain MRI; and concluded that, WMH may serve as a surrogate marker for the effect of vascular risk factors on cognitive abilities in PD. These findings will support the need to adopt routine vascular risk factors screening for our PD patients, in order to identify the modifiable vascular risk factors early.

In this survey, even though non-significant, the proportion of patients with subjective complaint of forgetfulness and hallucination were higher in WMH group compared to those with normal MRI. These findings were consistent with plethora of scientific evidences which indicates high prevalence of cognitive impairment/ or dementia and neuropsychiatric symptoms in PD patients with high burden of WMH (5, 15–21). These results support the need to routinely screen PD patients for cognitive impairment and comorbid psychiatric disorders; as early identification and treatment of PD dementia is associated with better quality of life in PD patients (21).

In present study, the overall prevalence of hypovitaminosis was high; however, no association was observed with WMH compared to those with normal brain MRI. In the recent decades, increasing scientific evidences have suggested possible association between hypovitaminosis D and PD; low vitamin D level has been associated with endothelial dysfunction which may play a role in the pathogenesis and progression of PD (12, 22). Moreover, studies have reported reduced plasma vitamin D levels were associated with low mini mental state examination (MMSE) scores in patients with Alzheimer's disease (AD) associated dementia and non-AD dementias (23, 24). These results further support the need of conducting future well designed controlled studies to investigate these observational results; as hypovitaminosis D is one of the easily reversible metabolic disorders. The limitation of this study includes: small sample size; lack of healthy control group for comparison of the findings; lack of using cognitive assessment batteries.

In summary, the present study indicates advanced age and dyslipidemia were associated with increased risk of having white matter hyperintensity on brain MRI of Ethiopian PD patients compared to those patients with normal MRI. Even though non-significant, the trend of vascular risk factors was in line with WMH. We recommend conducting future controlled study to consolidate our findings.

Abbreviations

AAU

Addis Ababa University; **CHS**:College of Health Science; **WMH**:White matter hyperintensity

CNS
Centeral Nervous System; **MRI**:Magnetic resonance image; **YSC**:Yehuleshet Specialty Clinic

Declarations

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Patient consent to publication: Not applicable

Ethical considerations:

The study received ethical approval from City Government of Addis Ababa Health Bureau Ethical Clearance Committee (Protocol number: A/A/HB/3510/227). All subjects provided written and verbal consent before conducting the interview. All the methods in the present study were performed in accordance with the relevant guidelines and regulations.

Availability of data and materials:

All data sets on which the conclusions of this manuscript rely are available as spread excel sheet document and available from the corresponding author on reasonable request.

Funding:

None

Conflict of interest:

All the authors have declared no conflict of interest.

Author's contribution:

BAA conceptualized, analyzed, interpreted, and was a major contributor in writing the manuscript. HG participated in data collection process mainly the demographic and PD-related clinical data. MZ analyzed and interpreted the clinical data regarding Parkinson's disease. YT extracted, analyzed, and interpreted data regarding neuroimaging findings. GZ conceptualized, analyzed, and interpreted both clinical and imaging data. All authors read and approved the final manuscript.

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Figures

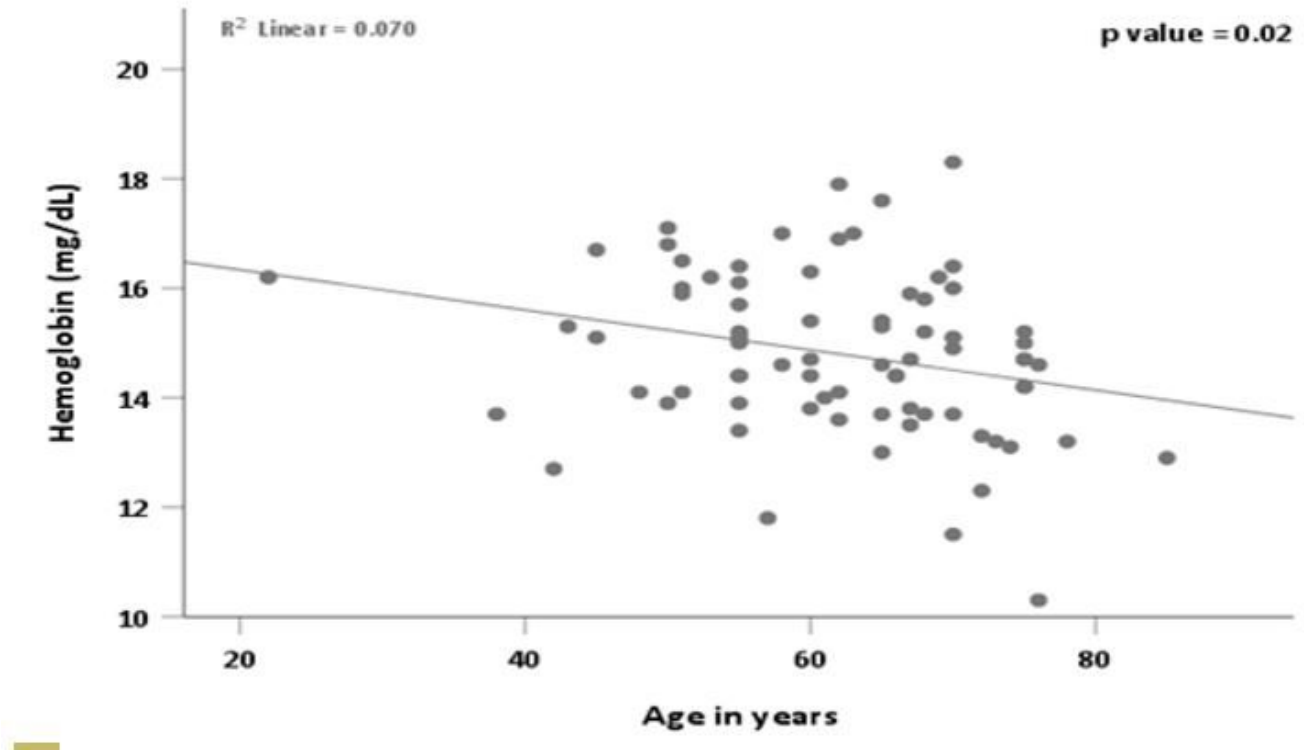

Figure 1

Line graph showing as age increases hemoglobin level decreases in the study participants.

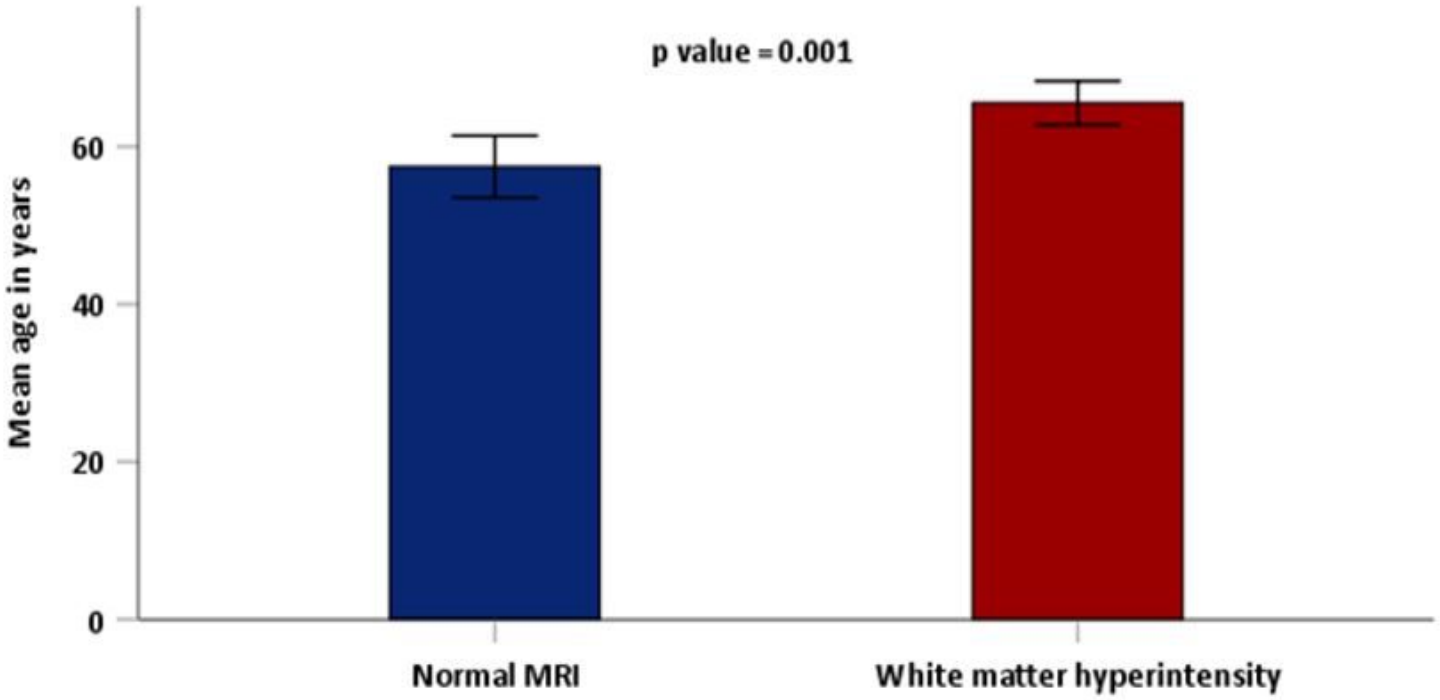

Figure 2

Bar graph showing significant assocaition between advanced age and white matter hyperintensity