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ORIGINAL ARTICLE

ASSOCIATION OF 99MTC- HMPAO SPECT MEASURED REGIONAL CEREBRAL BLOOD FLOW AND SERUM VITAMIN D LEVEL WITH CLINICAL STAGING OF PARKINSON'S DISEASE

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Abstract:

Background: *Parkinson's disease (PD) is the most common neurodegenerative movement disorder. Diagnosis of PD can be made through Single-photon emission computed tomography (SPECT). Vitamin D deficiency has recently been proposed as a potential risk factor for PD. This study aimed to evaluate the association of ^{99m}Tc- HMPAO SPECT image findings and vitamin D status with clinical staging of PD.* ***Methods:*** *This cross-sectional study was conducted in Department of Neurology, Sir Salimullah Medical College Mitford Hospital for a period of 12 months. Total 66 diagnosed PD patients were included after taking informed written consent. Detailed demographic history and neurological examination were done. The severity of PD was assessed using the modified Hoehn and Yahr (H & Y) scale. Serum 25-Hydroxyvitamin D level was measured for each participant. ^{99m}Tc- HMPAO SPECT imaging was done at Institute of Nuclear Medicine and Allied Sciences.* ***Results:*** *The mean age of the studied respondents was 71±8.72 (SD) years wherein maximum were male (59.1%) and aged above 70 years. The most common symptoms among the patients were tremor (78.8%) and bradykinesia (75.5%).The mean duration of PD was 5.74±2.22 (SD) years. Majority of the patients were diagnosed to have stage-2 (30.3%) followed by stage-2.5 (24.2%), stage-3 (16.7%), stage-4 (7.6%), stage-1 (4.5%), and stage-5 (3%). As the clinical stage of PD advanced from stages 1-5, the HMPAO uptake reduced significantly in the basal ganglia (p=0.006) .Vitamin-D level decreased significantly as the disease severity progress from stage-1 (27.8 ng/ml) to stage-5 (19.5 ng/ml) (p-value=0.008).* ***Conclusion:*** *Serum Vitamin-D level was inversely associated to severity of PD and decreased regional cerebral blood flow in basal ganglia in advanced stages of PD patients. However, further larger study is recommended.*

Keywords: *Parkinson's disease, 99mTc HMPAO SPECT, Regional cerebral blood flow, Serum vitamin D level.*

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Introduction:

Parkinson's disease (PD) is a common neurodegenerative disorder that can cause major incapacity and lessened class of life[1]. It is the second most common neurodegenerative disease worldwide with incidence and prevalence on the rise along with changing population demographics[2].The prevalence of PD in industrialised countries is generally estimated at 0.3% of the entire population and about 1% in people over 60 years of age [3]. PD is rare before 50 years of age, but the incidence increases 5–10-fold from the sixth to the ninth decade of life [4]. It is found that relative risk in first-degree relatives of PD cases increases by approximately two- to three-fold[5].

There are several proposed mechanisms for neuronal death in PD; however, not all of them are well understood. Five proposed major mechanisms for neuronal death in Parkinson's disease include protein aggregation in Lewy bodies, disruption of autophagy, changes in cell metabolism or mitochondrial function, neuroinflammation, and blood-brain barrier (BBB) breakdown resulting in vascular leakiness[6].

At present, the diagnosis of PD still depends mainly on clinical criteria. But the insidious onset and multifarious presentations often interfere with the accuracy of PD diagnosis, therefore, a considerable misdiagnosis in PD patients is inevitable[7]. The pathophysiological changes in PD start to occur before the onset of clinical symptoms. Motor disturbances are known to occur only after about 50% to 60% of striatal dopamine is lost. Brain single-photon emission tomography (SPECT) imaging with specific radioligands provides a useful tool of in vivo investigation of the pathogenesis of PD, and it is a sensitive method for examining the integrity of the presynaptic dopaminergic system[8].99mTc HMPAO is a lipophilic compound that easily crosses the blood brain barrier and is therefore taken up on first pass through the brain where it is retained for several hours. It is distributed in proportion to regional cerebral blood flow[9]. SPECT is an imaging modality that is capable of differentiating between PD and essential tremor[10] .SPECT imaging can also distinguish between PD and drug-induced Parkinsonism[10,11]. However, any disease that causes loss of the presynaptic dopamine neurons will appear as abnormal compared with normal controls in SPECT. Thus, SPECT is not able to differentiate among PD, progressive supranuclear palsy, multiple system atrophy, and other neurodegenerative disorders that affect the dopamine neurons[12]. SPECT is now well recognized and documented thoroughly in terms of its sensitivity in detection of PD. But there still remains paucity of data on correlation of SPECT imaging with clinical staging of PD[13, 14, 15].

Recently, vitamin D is not only considered as a vitamin, but also as a hormone with autocrine and paracrine functions well beyond those of regulating calcium homeostasis and bone health. Optimal balance, muscle strength, and innate immunity require sufficient vitamin D levels, and its deficiency is correlated with increasing risk for various types of cancer, as well as autoimmune and cardiovascular disorders[16]. Recently, chronic inadequacy of vitamin D intake has been suggested to play a remarkable role in the pathology of Parkinson's disease[17]. Related to the role of vitamin D and PD, there are some cross-sectional studies in Japan indicating that serum levels of 25-hydroxyvitamin D (25OHD) as well as 1, 25-hydroxy-vitamin D (1, 25OHD) may have an inverse correlation with the severity of PD[18,19], and higher circulating 25OHD levels are significantly related to milder form of PD[20]. This observation has been confirmed in a European Caucasian population showing a significant decline in vitamin D levels in patients with PD compared with healthy controls[21]. In a post hoc analysis of more than 3000 participants in Finland, higher serum vitamin D level was associated with lower risk for PD[17].Fahmy et al. found that there was an association between low vitamin D levels and PD[22]. It seems that the distribution of vitamin D receptors in the substantianigra is widely known to be affected in PD, and the involvement of this vitamin has been revealed in the regulation of tyrosine hydroxylase gene expression and consequently dopamine biosynthesis[17,23]. However the epidemiological evidence of an association between vitamin D and Parkinson's disease is limited. Therefore, considering the circumstances this study was taken for evaluation of 99mTc- HMPAO SPECT image findings and vitamin D status with clinical staging of Parkinson's disease.

Methods:

Study design, population and settings:

This study was carried out in the Department of Neurology at Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh, from July 2021 to June 2022. The study included 66 patients with Parkinson's disease (PD) .Subjects were selected based on inclusion and exclusion criteria. The patient was incorporated after receiving written approval. Aged 18 years or older, the included patients underwent a neurologist's examination, and Parkinson's disease was diagnosed clinically by MDS clinical diagnostic

criteria. Patients with parkinsonism other than Parkinson's disease, osteoporosis or taking a vitamin D supplement, pregnant women or lactating mothers, carcinoma, chronic kidney disease, chronic liver disease, and hypoparathyroidism were all excluded from the study. The study protocol received approval from the ethical council of the Sir Salimullah Medical College in Dhaka, Bangladesh.

A total of 66 patients with Parkinson's disease attending the outpatient department and indoor department of neurology at Sir Salimullah Medical College Mitford Hospital were enrolled in this study. The patient's parkinsonism was diagnosed by the primary physician in the outdoor and indoor departments. Then patients with Parkinson's disease were diagnosed clinically by the researcher himself using MDS clinical diagnostic criteria for Parkinson's disease. Each participant provided written, informed consent. Then patients were subjected to a detailed neurological examination, and a modified Hoehn and Yahr (H & Y) scale was used for the clinical staging. Then, serum vitamin D levels were measured for all the patients using the enzyme-linked immunosorbent assay (ELISA) technique. Venous blood samples were collected and then centrifuged to get serum. The quantitative measurement of total 25-OH vitamin D3 in serum was done using the competitive immunoassay technique (Advia CentaurR XPT Immunoassay System, Siemens) . After that, all the patients underwent a SPECT scan at the Institute of Nuclear Medicine and Allied Sciences, Dhaka Medical College Hospital campus, Dhaka. A brain perfusion study was performed 30 min after intravenous administration of a 10 mci dose of 99 mTc Medi-Exametazime (HMPAO). Dynamic sequential SPECT images were taken from the vertex through the skull base for 30 minutes in 28 seconds/frame, Matrix: 128×128. Image interpretation was done by visual and quantitative analysis in transaxial, coronal, and sagittal slices by the Siemens-Symbia T16 dual headed SPECT-CT. Semi quantitative analysis was performed by comparing uptake in the area under investigation with uptake in the area unaffected by the disease process. The cerebellum is pathologically relatively spared in Parkinson's disease, and therefore it is usually used as the reference region in SPECT studies in Parkinson's disease. We expressed HMPAO uptake for each region as the ratio of uptake in that region to that in the cerebellum. All the collected information was stored in separate data records.

Data collection and laboratory procedures:
Data on the patient's sociodemographics, clinical features, stroke risk factors, and pertinent laboratory tests will be performed and recorded when the patient is included in the study.

All information was collected and documented, including demographic data (age and gender), DSA and MRA were given for each case; the neurologist was blind to the modality of angiography; and the order of DSA and MRA results were randomized. Case Report Forms were used to collect and record all of the data (CRF).

Data management and analysis:
Data were collected, tabulated, and analyzed by SPSS version 24.0. Socio-demographic characteristics, laboratory parameters, and 99mTc-HMPAO SPECT Imaging findings were reported. Continuous data were expressed as mean and standard deviation, and categorical data were expressed as frequency and percentage. Associations were assessed by student t-tests and one-way ANOVA tests for continuous variables, where applicable. Probability (p) values of < 0.05 were considered statistically significant. The correlation was seen by Pearson's correlation coefficient test.

Results:
This study was a cross-sectional study conducted in Department of Neurology, Sir Salimullah Medical College. A total of 66 patients diagnosed to have PD by the generally accepted clinical criteria were included in this study.

Table-4.1

Distribution of socio-demographic characteristics among the patients with Parkinson's disease (PD) (n=66).

Variable	Frequency N	Percentage (%)
Age group (in years)		
50-60	11	16.7
61-70	14	21.2
70-80	34	51.5
>80	7	10.6
Age		
Mean ±SD	71±8.72	
Gender		
Male	39	59.1
Female	27	40.9
Residence		
Rural	36	54.5
Urban	30	45.5

More than half of the patients with PD were from the age group above 70 years(51.5%) and the mean age was 71±8.72 years and majority of the patients with PD were male (59.1%).54.5% patients were from rural area and 45.5% patients were from urban area (Table-I).

Table-II

Distribution of co-morbidities, family history and duration of PD among the study population (n=66)

Variables	Frequency N	Percentage (%)
Duration of PD(in years)		
Mean ±SD	5.74±2.22	
Co-morbidities		
DM	14	21.2
HTN	16	24.2
Family history of PD		
Yes	6	9.1
No	60	90.9
History of exposure to insecticides		
Yes	5	7.5
No	61	92.5

The mean duration of PD was 5.74±2.22 years and 24.2% and 21.2% of the patients had HTN and DM respectively. About 9.1% were reported to have a family history of Parkinson's disease in their family and 7.5% have been exposed to some sort of insecticides (Table II).

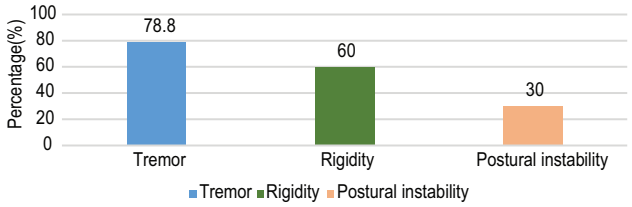


Figure-1: *Distribution of cardinal symptoms among the PD patients in addition of bradykinesia (n=66)*

The most common symptoms were tremor (78.8%) along with bradykinesia. Rigidity and postural instability was observed in 60% and 30% of the patients respectively (Figure 1.

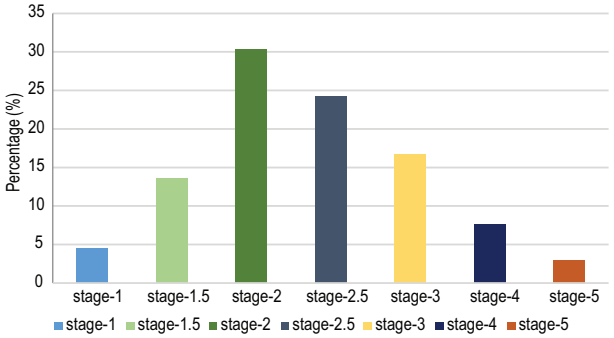


Figure-2: *Distribution of the patients of Parkinson's disease according to clinical stages. (n=66)*

Out of 66 PD patients, 12 patients were diagnosed with stage-1 and 1.5 (stage-1:4.5% and stgae1.5-13.6%), 36 patients were diagnosed with stage-2 and 2.5 (stage-2:30.3% and stage-2.5:24.2%), 11 patients were diagnosed with stage-3(16.7%), 5 patients were diagnosed with stage-4 (7.6%) and 2 patients were diagnosed with stage-5(3.0%) (Figure 2).

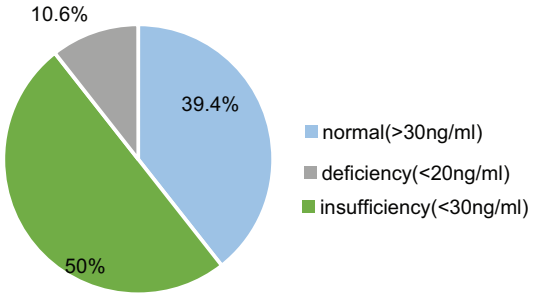


Figure-3 *Distribution of 25(OH) D level among the PD patients (n=66)*

Among the PD patients majority of the patients had vitamin D insufficiency (n=33,50%) and 10.6% (n=7) had vitamin D deficiency .39.4%(n=26) was reported to have vitamin D within normal level (Figure 3).

Table-III

Exposure to sun and 7 days dietary recall chart of vitamin –D rich foods (n=66)

Variables	Patients with normal vitamin-D leveln=26 n(%)	Patients with vitamin-D insufficiency/deficiency n=40 n(%)	p-value
Sun exposure			0.032
sun exposure > 30 minutes/day	21(80.8)	22(55)	
sun exposure < 30 minutes/day	5(19.2)	18(45)	
Vitamin-D rich foods(_>2 days per week)			
Meat	14(53.8)	18(45)	0.482
Organ meat	18(69.2)	17(42.5)	0.033
Fish	16(61.5)	15(37.5)	0.056
Milk and dairy products	16(61.5)	17(42.5)	0.131
Eggs	14(53.8)	13(32.5)	0.085
>_2 vitamin-D rich foods>_2 days within last 7 days		0.018	
Yes	20(76.9)	19(47.5)	
No	6(23.1)	21(52.5)	

*p-value obtained by chi-square test

PD patients who were less exposed to sun (45%) and lower intake of vitamin-D rich foods (52.5%) had higher in vitamin-D insufficiency/deficiency in compared to patients with normal vitamin-D level (Figure 3).

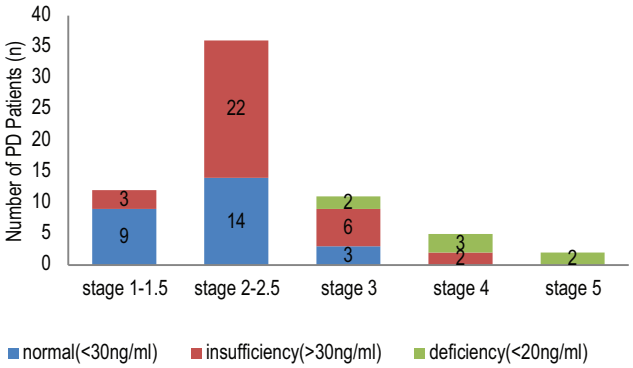


Figure-4 *Distribution of serum 25 (OH) D level among the patients of different clinical stages of PD (n=66)*

Figure 4 depicts the number of PD in each clinical stage with vitamin D insufficiency, deficiency and normal level. Out of 12 patients with PD stage 1-1.5,3 had vitamin D insufficiency and 9 had normal level of vitamin D. Out of 36 patients with PD stage 2-2.5, 22 had vitamin D insufficiency and 14 had normal level of vitamin D. Among stage 3 PD patients, 2, 6, 3 had vitamin D deficiency, insufficiency and normal respectively. Moreover among stage 4 and 5, 3 and 2 patients had vitamin D deficiency respectively.

It is seen from figure-5 that the 25(OH) D levels has a inversely proportional relationship with the severity in different clinical stages of PD patients. The median (IQR) vitamin D level (expressed in ng/ml) was 30(24-31), 28(25.5-31), 28(27-29), 28.7(25.4-31), 24.9(24-28.8), 19.8(19-21.9) and 19(18.5-19.5) for stage-1 stage-1.5, stage-2, stage-2.5, stage-3, stage-4 and stage-5 respectively.

Table-IV : *Univariate Logistic regression analysis of vitamin-D deficiency with age, gender, sun exposure, less intake of vitamin-D rich foods*

Variables	Odds ratio	95%CI (Lower-upper)	p-value
Age	0.84	0.26-2.74	0.767
Gender	1.14	0.35-3.66	0.822
sun exposure <30 minutes/day	2.93	0.84-10.3	0.093
Lower intake of vitamin-D rich foods	4.09	1.21-13.8	0.023

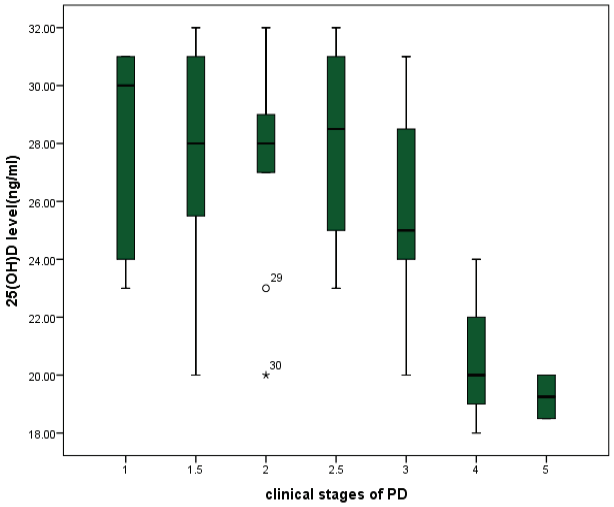


Figure-5: *Box-plot diagram between serum 25(OH)D level and clinical stages of PD.*

Logistic regression analysis revealed that age, sex and sun exposure <30 minutes/day did not contribute significantly to the serum vitamin D status, whereas lower intake of vitamin D rich foods affected significantly as negative factors (Table IV).

Table-V: *Mean ±SD of serum vitamin 25(OH)D level among the patients with different clinical stages of PD (n=66)*

Clinical stage of PD	25(OH)D level Mean ±SD(in ng/ml)	p-value*
Stage-1	27.8±3.96	0.001
Stage-1.5	27.6±3.31	
Stage-2	27.5±3.57	
Stage-2.5	26.4±3.16	
Stage-3	25.9±3.53	
Stage-4	20.6±2.41	
Stage-5	19.5±1.07	

*p-value obtained by one way ANOVA

From table-III it was observed that the mean 25(OH) D level was the higher in the earlier stages of patients of PD, which is (stage-1-2.5:27.8-26.4 ng/ml) and lower in more advanced stages of PD (stage-4-5:20.6-19.5 ng/ml).Stages of PD was significantly associated with the level of 25(OH) D level (p-value: 0.001) (Table V).

Table-VI : *Mean (SD) regional cerebral blood flow measured by HMPAO SPECT in different cerebral regions.*

Cerebral regions	Right Mean ±SD	Left Mean ±SD	p-value*
Basal ganglia	**0.83±0.07	0.82±0.08	0.473
Occipital	0.81±0.06	0.82±0.04	0.983
Parietal	0.77±0.12	0.76±0.10	0.446
Frontal	0.71±0.06	0.72±0.07	0.500
Temporal	0.75±0.12	0.74±0.10	0.221
Thalamus	0.74±0.22	0.73±0.23	0.967

*p-value obtained by student t-test.
**Ratio of regional cerebral blood flow in comparison to cerebellum

There were no significant differences between HMPAO uptake in the right and left hemispheres in all the regions (Table VI).

Table-VII : *Comparisons of mean (SD) regional cerebral blood flow measured by HMPAO SPECT in different regions with clinical stages of PD.*

Cerebral regions	Stage-1-1.5 Mean±SD	Stage-2-2.5 Mean±SD	Stage -3 Mean±SD	Stage-4-5 Mean±SD	Mean±SD p-value*
Basal ganglia	**0.86±0.06	0.83±0.08	0.77±0.05	0.70±0.05	0.006
Occipital	0.84±0.04	0.82±0.55	0.81±0.09	0.76±0.14	0.254
Parietal	0.80±0.08	0.76±0.11	0.73±0.13	0.68±0.15	0.238
Frontal	0.74±0.06	0.72±0.06	0.67±0.06	0.67±0.56	0.995
Temporal	0.75±0.11	0.77±0.09	0.71±0.13	0.67±0.11	0.773
Thalamus	0.72±0.24	0.76±0.22	0.71±0.25	0.72±0.15	0.922

*p-value obtained by one-way ANOVA.

**Ratio of regional cerebral blood flow in comparison to cerebellum

From table-V It is seen that as the clinical stage of PD advanced from stages 1-5, the HMPAO uptake reduced significantly in the basal ganglia (p=0.006). There was no significant reduction in the occipital, parietal, frontal, temporal region and thalamus (Table VII).

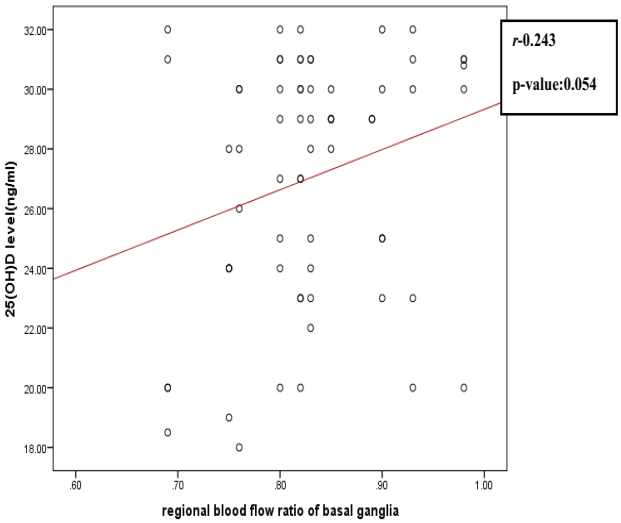
Table-VIII

Comparisons of mean (SD) regional cerebral blood flow measured by HMPAO SPECT in basal ganglia with clinical stages of PD

Clinical stage of PD	Ratio of regional cerebral blood flow in comparison to cerebellum (Mean ±SD) (in ng/ml)	p-value*
Stage-1-1.5	0.86±0.06	0.006
Stage-2-2.5	0.83±0.8	
Stage -3	0.77±0.05	
Stage-4-5	0.70±0.05	

*p-value obtained by one way ANOVA

From table-4.8 It is seen that as the clinical stage of PD advanced from stages 1-5, the HMPAO uptake reduced significantly in the basal ganglia (p=0.006) (Table VIII).



p-value obtained by Pearson's correlation co-efficient test.

Figure-6 *Scatter-plot diagram of correlation between vitamin D and regional blood flow ratio of basal ganglia.*

From figure-6, It is observed that there was a insignificant correlation between the 25(OH) D level and the regional blood flow in basal ganglia (p-value:0.054).

Discussion:

In recent years, PD has undergone the fastest growth in prevalence and disability among neurological disorders, and it has become one of the leading causes of disability worldwide[24]. The Global Burden of Disease study reported that incident cases of PD were 1.02 million in 2017 [25] (James et al. 2018).The aim of this study was to assess the influence of different clinical stages of Parkinson's disease on the vitamin D levels and correlation $^{99m}T_{c-}$ HMPAO SPECT Imaging findings with different clinical stages. In the present study it was observed that most of the study population was above the age of 50 years with highest number of patients in the age group 70-80 years and male (59.1%) were predominantly reported to have Parkinson's disease than females (40.9%) in this study. The incidence of Parkinson's disease increases steeply with age especially after age 60 years, and men have higher incidence than women, except for ages 80–99 years making age one of the crucial risk factor for the disease[26]. PD data collected from global burden of disease 2019 also agreed with the findings of our study where it was reported that the largest number of PD patients was seen in the groups aged more than 65 years, and the percentage rapidly increased in the population aged more than 80 years [27].

Family history is another strong risk factor for development of PD. Balestrino et al. reported that familial forms of PD accounts for only 5%–15% of patients with Parkinson's disease [5]. A cross-sectional study among 100 PD patients reported 6.3% of the PD reported family history of Parkinson's disease, 23.9% reported diabetes mellitus and 21.7% reported history of hypertension among Parkinson's disease patients[28] (Sarkar et al. 2019). The current study was in agreement with these findings since 9.1% of study population reported a family history of PD, 24.2% and 21.2% of the patients had HTN and DM respectively. In this study most of the patients were in stage 1 - 2.5 (72.6%), followed by stage 3 (16.7%), and stage 4-5 (10.6%).In a previous clinical study of 135 patients, 55.56% were in stage 1-2.5,31.11% patients were in stage 3 and 13.33% patients were presented at stage 4-5 [29] .

In our study, majority of patients had vitamin D insufficiency (n=33, 50%) and deficiency . Previously in a double-blinded cross-sectional study among 109 PD 38.4% of the patients showed deficiency level of 25(OH)D and 72.8% showed 25(OH)D level insufficiency[30].This study observed that PD patients who were less exposed to sun (45%) and lower intake of vitamin-D rich foods (52.5%) had higher in vitamin-D insufficiency/deficiency in compared to patients with normal vitamin-D level . In a previous case-control study PD patients who were less exposed to sun had decrease vitamin D level[31].In the present study, we observed that the more advanced stage of PD was significantly associated with lower level of 25OHD (stage-1-27.8ng/ml vs stage-5-19.5ng/ml). On the other hand, Fahmy et al. found that mean serum vitamin D level was significantly lower in PD patients compared to healthy controls (p-value= 0.029) however no significant difference was found between disease stages as regards to mean serum 25 vitamin D level (p-value= 0.372)[22].

In the current study it was observed that HMPAO SPECT indicated a significant decrease in regional blood flow in the basal ganglia (p-value: 0.006) with the advancement of PD from stages1-5. This is consistent with a cross-sectional study conducted among 21 Parkinson patients and 11 controls were it was reported that the uptake of HMPAO by the basal ganglia (p-value: 0.004) was significantly decreased in the PD patients compared with normal controls[32]. In contrast another study conducted among 16 Parkinson's patients failed to demonstrate consistent alteration in blood flow in the basal ganglia (Spampinato et al. 1991). The discrepancies in the findings may be due to the fact that basal ganglia uptake was measured visually resulting on underestimation of the reduction in uptake. A study conducted in South Korea among 10 Parkinson's disease patients showed a significant reduction in ratio of uptake of HMPAO of frontal region ($p<0.05$)[33] which was not similar with the finding in the present study .In this study, we found insignificant correlation between serum vitamin D level and regional cerebral blood flow in parkinson's disease patients. But there is a previous study, where positive correlation between vitamin D deficit and impaired regional cerebral blood flow was seen in neurodegenerative disease[34].

Conclusion:

This study concludes that serum vitamin D level was inversely associated to severity of PD.99mTc HMPAO SPECT image findings showed significantly decreased regional cerebral blood flow in basal ganglia in advanced stages of PD patients. No significant correlation was found between serum vitamin D level and regional cerebral blood flow in basal ganglia.

Limitations:

All samples were collected from a single centre. DaTscan based SPECT is now widely used for detection of PD .Which is not available in our country.

Data Availability:

The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study

Funding:

Funding from research grant from Bangladesh Medical Research Council (BMRC) was received for this study.

Ethical consideration:

The study was conducted after approval from the ethical review committee of Sir Salimullah Medical College. The confidentiality and anonymity of the study participants were maintained.

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