HYPOVITAMINOSIS D, CORTICAL AND SUB-CORTICAL COGNITIVE FUNCTIONING DEFICITS IN PATIENTS WITH PARKINSON'S DISEASE DEMENTIA

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ABSTRACT

Objective: To examine vitamin D status and its association with cortical/sub-cortical cognitive functioning in patients with Parkinson's Disease Dementia.

Study Design: Cross sectional study.

Place and Duration of Study: Bahawal Victoria Hospital, Civil Hospital and Nishter Hospital Pakistan during May 2016 to June 2017.

Material and Methods: Fifty patients diagnosed with PDD at Bahawal Victoria Hospital, Civil Hospital and Nishter Hospital Pakistan during May 2016 until June 2017 and fifty healthy individuals participated in the study. Blood samples were examined for serum 25 hydroxy vitamin D. Following, Parkinson's disease cognitive rating scale was administered to assess cortical and sub-cortical cognitive functioning.

Results: Results showed that patients with PDD were deficient in serum 25 hydroxy vitamin D and cortical/subcortical cognitive functioning in contrast with healthy individuals. Serum 25 hydroxy Vitamin D and education level of patients with PDD were significant predictors of cortical and subcortical cognitive impairment.

Conclusion: Hypovitaminosis D is a biomarker of cortical and subcortical cognitive deficits in patients with PDD.

Keywords: Cognition, Dementia, Parkinson's disease, Vitamin D.

INTRODUCTION

Vitamin D deficiency has become a serious health concern in Asia[1,2]. Sufficient levels of vitamin D are essential for bone health and muscle function[3]. Recent studies demonstrated that inadequate vitamin D levels increase risk of cognitive impairment, Alzheimer's disease and dementia[4,5]. Vitamin D receptors and the enzyme (1alpha-hydroxylase) which is responsible for formation of active vitamin D are wide spread across neurons, glial cells, hypo-thalamus and dopaminergic neurons of substantia nigra in human brain[6]. Vitamin D regulates nerve growth factor which is a vital molecule for neuronal survival of the cortical and hippocampus neurons[7]. Vitamin D has neuroprotective effects by abolishing (i) β amyloid-induced calcium elevation (ii) toxicity that hamper release of nerve growth factor in cortical neurons. β amyloid deposits not only suppress expression of vitamin D receptors rather induce neuro degeneration in vitamin D receptor pathways[8]. Vitamin D exerts neuroprotective effects on nervous tissues by modulating production of neurotrophin, synthesis of neuromediators, intracellular calcium homeostasis, and deterrence of oxidative stress[9]. Hypovitaminosis D is a risk factor for several neurological diseases including Alzheimer's disease, Parkinson's disease (PD), dementia and multiple sclerosis[10]. It works as immunomodulatory agent by decreasing the production of proinflammatory cytokines, enhancing secretions of immunosuppressive IL-10 cytokine and inhibiting the development of T-regulatory cells[11]. Meta-analysis of studies indicates that severe vitamin D deficiency (<25nmol/L) increases the risk of dementia and cognitive deterioration[12,13]. Previous studies have shown an association between cognitive impairment in PD with lower serum vitamin D[14,15] but there is a gap in literature to understand whether cortical and subcortical cognitive functioning is vulnerable to vitamin D levels in PDD. To this end, authors designed the current study to examine cortical

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cognitive functions in patients with Parkinson's disease dementia (PDD). Prefrontal cortex and hypothalamus are involved in higher order cognitions and memory. Given that functioning of cortical neurons in prefrontal cortex and hypothalamus are most affected by vitamin D status, it was hypothesized that patients with PDD would demonstrate impaired cortical cognitive functioning in contrast with healthy controls. The current study was designed with the objective to: (i) compare serum 25 hydroxy vitamin D and cortical/ subcortical functioning between patients with PDD and healthy control individuals (ii) assess the relationship between serum 25 hydroxy vitamin D and cortical/ subcortical cognitive functioning in patients with PDD.

MATERIAL AND METHODS

The study had cross sectional research design and was approved by board of studies of the Islamia University of Bahawalpur. All participants and their caretakers gave written informed consent. Convenience sampling was used in the study. Fifty patients diagnosed with PDD at Bahawal Victoria Hospital, Civil Hospital and Nishter Hospital during May 2016 until June 2017 participated in the study. The clinical dementia rating-CDR[16] was used to identify mild dementia (score 1) in patients. The inclusion criterion for patient group were: (i) age range 60-85 years (ii) able to understand instructions and complete assessment (iii) willing to provide medical record. The exclusion criterion for patient group were: (i) history or present symptomology of stroke, Alzheimer's disease, epilepsy, use of vitamin D supplements, moderate or severe dementia. Fifty healthy demographically matched individuals (control group) from community took part in the study. The exclusion criterion for control group were: (i) history or present symptomology of stroke, Alzheimer's disease, epilepsy, use of vitamin D supplements, no dementia as screened through CDR score zero[16]. Blood samples were collected early morning after at least 8 hour overnight fasting for examination of serum 25-hydroxy vitamin D. Reference values indicates vitamin D deficiency = <20 ng/mL; insufficiency 21-29 ng/ mL; sufficient = or >30 ng/mL[17]. Then partici-pants were administered Parkinson's disease cognitive rating scale[18] was to assess cortical and subcortical cognitive functioning. This scale has been designed according to neural correlates of cognitive functions. Subcortical cognitive functions are attention, working memory, clock drawing, alternating, action verbal fluencies, immediate/delayed verbal memory. Cortical cognitive functioning is assessed through confrontation naming task. Total score ranges from 0 to 134; high scores represent better performance. Scale is highly reliable and valid. Following, subjects were thanked for their participation.

Statistical Analysis

Demographic data was analyzed through descriptive statistics. Independent sample t-test was used to compare means. Repeated measures analysis of variance (ANOVA) was used to examine group differences on cortical/subcortical cognitive functions with factor 9 (attention vs. working memory vs. unprompted clock drawing vs. alternating vs. action verbal fluencies vs. immediate free recall verbal memory vs. delayed free recall verbal memory vs. confrontation naming vs. total PD-CRS scores) x group 2 (patients with PDD vs. healthy controls). Regression analysis was conducted to identify predictors of cognitive functioning in PDD with factors: total PD-CRS scores as dependent and serum vitamin D levels, disease duration, disease onset, age, gender, socioeconomic class, and education as independent variables. A *p*-value of 0.05 was considered significant.

RESULTS

Fifty patients with PD and fifty healthy individuals were compared. Demographic characteristics showed that there was no significant difference on age between both groups. Percentage on gender, education, and socioeconomic status revealed no difference between groups (table). However, patients had

lower serum 25-hydroxy vitamin D levels as compared with healthy individuals. Disease onset and duration were also reported in table. ANOVA showed significant main effects of cognitive functioning F (8,98)= 14347.49, p <0.0001, ηp2=0.99, immediate free recall (M ± SE 6.89 ± 0.13), sustained attention (M ± SE 5.98 ± 0.09), working memory (M ± SE 6.89 ± 0.13), unprompted clock drawing (M ± SE 6.05 ± 0.22), delayed free recall verbal memory (M ± SE 6.51 ± 0.11), alternating verbal fluency (M ± SE 11.82 ± 0.11), action verbal fluency (M ± SE 18.37 ± 0.14), confrontation naming (M ± SE 11.84 ± 0.12), total PD-CRS scores (M ± SE 73.22 ± 0.45) and group F (1, 98)= 8171.42, p <0.0001, η p2=0.98, PDD (M + SE 7.08 + 0.14) controls (M + SE 25.45 + 0.14). There was a significant interaction between cognitive functioning x group F (8, 98)= 4582.45, p<0.0001, ηp2=0.97 (see table for mean scores). Regression analysis showed significant model R^2 = 0.59, F (7,49) = 8.81, p<0.001, vitamin D levels standardized β= 0.78, t= 7.17, p<0.001; education β=0.25, t= 2.27, p<0.05 whereas gender β= 0.12, t=1.15, p= 0.25; socioeconomic class β= 0.02, t= 0.24, p= 0.81; age β= 0.04, t=0.43, p=0.66; disease duration β=0.00, t=0.07, p=0.94; age onset β= 0.15, t=1.35, p=0.18 failed to reach level of significance. There were few important results: (i) Patients with PDD had vitamin D deficiency in contrast with healthy controls (ii) Cortical/ subcortical cognitive functioning was impaired in patients with PDD in contrast with healthy controls (iii) serum 25 hydroxy vitamin D and education level in patients with PDD were found as significant predictors of cognitive performance in PDD.

Table: Characteristics of sample.

	PDD		**Controls**		
	n		n		
	50		50		
Gender m/f	(25%/25%)		(25%/25%)		
Social class					
High	17 (17%)		17 (17%)		
Middle	20 (20%)		20 (20%)		
Low	13 (13%)		13 (13%)		
Education					
Graduation & above	20 (20%)		20 (20%)		
O Level-Graduation	20 (20%)		20 (20%)		
Below O Level	10 (10%)		10 (10%)		
	M ± SE	LB-UB	M ± SE	LB-UB	
Age (60-85 years)	74.20 ± 1.14		74.52 ± 9.97		t (49)=0.22, p=0.82
Disease duration	4.68 ± 9.29				
Disease onset	68.18 ± 9.34				
Serum 25-Hydroxy Vitamin D ng/mL	11.42 ± 9.34		36.80 ± 9.57		t (49)= 35.79, p<0.001
Immediate FR	3.94 ± 0.19	3.55-4.32	9.84 ± 9.19	9.45-10.22	
Sustained attention	2.82 ± 0.13	2.55-3.08	9.14 ± 9.13	8.87-9.40	
Working memory	2.34 ± 0.12	2.08-2.59	9.18 ± 9.12	8.92-9.43	
Unprompted CD	2.66 ± 0.32	2.02-3.29	9.44 ± 9.32	8.80-10.07	
Delayed FVM	2.36 ± 0.15	2.04-2.67	10.66 ± 9.15	10.34-10.97	
Alternating VF	4.38 ± 0.15	4.06-4.69	19.26 ± 9.15	18.94-19.57	
Action VF	8.32 ± 0.19	7.92-8.71	28.42 ± 9.19	28.02-28.81	
CN	5.06 ± 0.18	4.69-5.42	18.62 ± 9.18	18.25-18.98	
Total PD-CRS	31.88 ± 0.64	30.59-33.16	114.56 ± 9.64	113.27-115.84	

DISCUSSION

Vitamin D deficiency has become a serious health issue particularly due to its' significant classic role in bone density and muscle

function[1,2]. Besides, vitamin D has gained attention of researchers in previous years due to its' non-classic role in neuropsychological functioning[4,5]. Results of the present study are consistent with previous studies which suggested that vitamin D is essential for brain health[4]. Deficient vitamin D is a risk for brain pathology leading to dementia and Alzheimer's disease[5,10] because vitamin D receptors are widespread in brain areas responsible for learning, memory and higher order cognitions such as hypothalamus, forebrain etc[6]. The present study demonstrated that patients with PDD are deficient in vitamin D which is a significant predictor of cortical and subcortical cognitive impairment. Vitamin D modulates neuronal survival and exerts neuroprotective effects by releasing toxicity in cortical neurons[7,8]. Vitamin D inhibits T-reg cells production, oxidative stress, and maintains intracellular homeostasis of calcium[9,10]. Previous research have demonstrated that cognitive performance is deteriorated with deficient vitamin D in patients with PD[14,15], however it is noteworthy that none of the studies have examined vitamin D status in patients with PDD and its' relationship with cognitive decline.

CONCLUSION

In conclusion, results of the current study suggest that vitamin D deficiency is a biomarker of cortical and sub-cortical cognitive functioning impairment in patients with PDD. These results have implications in early detection of cortical and subcortical cognitive functioning in PDD with vitamin D status. Cognitive rehabilitation must be included in treatment plan for better patient care. Future studies must examine whether cortical/subcortical cognitive functions are improved with medicine in PDD.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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