Vitamin D and Focal Brain Atrophy in Parkinson's Disease With Non-dementia Patients: A Voxel-based Morphometric Study

Yingying Xu

Second Affiliated Hospital of Soochow University

Erlei Wang

Second Affiliated Hospital of Soochow University

Qilin Zhang

Second Affiliated Hospital of Soochow University

Kairu Ni

Second Affiliated Hospital of Soochow University

Jing Liu (✉ nnliujing181@126.com)

Second Affiliated Hospital of Soochow University

Weifeng Luo

Second Affiliated Hospital of Soochow University

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Abstract

Introduction: The importance of vitamin D in Parkinson's disease (PD) was explored, and vitamin D status has been suggested to influence cognition. Gray matter volume (GMV), a potential marker of cognitive function, was automatically segmented using voxel-based morphometry with SPM12 software. We investigated whether lower serum 25-hydroxyvitamin D level was associated with focal brain volume reduction in PD with non-dementia (PDND) patients.

Methods: Baseline neuropsychiatric performance and serum 25-hydroxyvitamin D levels were examined in 24 PDND patients and 24 healthy controls (HCs). A set of cognitive scales were used to evaluate the cognition. Voxel-based morphometry (VBM) was performed to calculate each PDND patient's GMV, based on structural magnetic resonance imaging data. Associations between serum 25-hydroxyvitamin D levels, cognition, and GMV were evaluated.

Results: The serum 25-hydroxyvitamin D levels of the PDND group were significantly lower than those of the HC group. The serum 25-hydroxyvitamin D levels of the PDND group were significantly lower than those of the HC group. The multiple linear regression analyses between serum 25-hydroxyvitamin D levels and the scores of subtests that analyzed cognitive function showed that serum 25-hydroxyvitamin D levels were negatively correlated with TMT-A scores and positively correlated with SDMT and AVLT scores. Multiple regression analyses showed that the right fusiform gyrus GMV positively correlated with serum 25-hydroxyvitamin D levels.

Conclusions: We found atrophy of the right fusiform gyrus with lower serum 25-hydroxyvitamin D level in PDND patients, and serum 25-hydroxyvitamin D level was closely positive associated with cognition. We hypothesized that the low serum 25-hydroxyvitamin D level in PDND patients might affect the auditory word learning ability by reducing the GMV in the right fusiform, leading to the decline of semantic understanding and memory function.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease among elderly individuals. An estimated 6.1 million individuals, globally, had a PD diagnosis in 2016, 2.4 times higher than the PD population in 1990(1). Cognitive impairment is one of the most common and important non-motor aspects of PD, which greatly affects function, quality of life, caregiver burden, and health-related costs. However, the etiology and pathogenesis of PD remain unclear. Recently, the importance of vitamin D deficiency in PD was explored, and Newmark proposed that a lack of vitamin D might be associated with PD pathogenesis(2). Vitamin D has been regarded as a neurosteroid that regulates immunomodulation and brain development and function in adulthood(3). Many areas of the brain, including the amygdala, hippocampus, thalamus, cortex, and substantia nigra, express both vitamin D receptor and 1 α -hydroxylase. Multiple lines of evidence have shown that vitamin D can be actively synthesized by

neurons and microglia. Furthermore, vitamin D status has been suggested to influence neurocognition(3–6).

Voxel-based morphometry (VBM) is a fully automated, whole-brain measurement technique that maps the statistical probability of differences in regional tissue volumes or densities between groups. Gray matter volume (GMV) is a marker of brain atrophy and a potential marker of cognitive function, based on VBM. GMV has been used to analyze differences in brain structure among different groups, in many studies, including PD(7, 8).

Karak is showed, in a large, community-based sample, that low 25-hydroxyvitamin D concentrations were associated with smaller hippocampal volumes and worse neuropsychological functions(9). In our previous study, serum vitamin D levels in PD patients were found to be significantly lower than those in controls, and vitamin D was found to have a protective effect on the cognitive functions of PD with non-dementia (PDND) patients.(10) Previous studies mostly focused on the changes of whole-brain volume, ventricular volume, and hippocampal volume, according to the vitamin D status(11, 12).The identification of focal brain atrophy has received little attention. Therefore, our objective, in this study, was to investigate the prospective correlations between serum vitamin D levels, cerebral GMV, and cognitive functions in PDND patients.

2. Materials And Methods

2.1 Participants

Eligible patients were recruited between January 2016 and March 2018 from the neurology clinic and the inpatient department of the Second Affiliated Hospital of Soochow University. All PDND patients were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria and the PDD diagnostic criteria, established by the International Movement Disorders Association, in 2007(13). The diagnosis of PDD needs to meet the following core features: (1) Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria. (2) A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as: (1) Impairment in more than one cognitive domain; (2) Representing a decline from premorbid level; (3) Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms. The patients were divided into PDND group, if they can't meet the criteria. For comparison, 24 sex- and age-matched healthy volunteers with similar levels of education were recruited as a control group.

The education levels of all participants were at least equivalent to the fourth-grade level which is the minimum level of education that can fulfill the assessment. Patients with other significant neurological diseases that affect cognition were excluded. Patients with abnormal liver and kidney function, thyroid disease, parathyroid disease or vitamin D supplements, were also excluded. This study was approved by

the Ethics Committee of the Second Affiliated Hospital of Soochow University. All subjects signed written informed consent prior to participation.

2.2 Clinical assessment

Demographic information and clinical characteristics were collected from all patients, including age at onset, sex, body mass index (BMI), disease duration, medical history, and medications. Levodopa (L-DOPA) equivalent dose (LED) was calculated for each patient⁽¹⁴⁾. Motor manifestations were evaluated using Unified Parkinson's Disease Rating Scale (UPDRS) part III scores and Hoehn-Yahr staging, in the "off" state. To evaluate the non-motor symptoms of PD, cognition was assessed by the Mini-Mental State Examination (MMSE). The Auditory Verbal Learning Test-Huashan Version (AVLT-H), digit span test (DST), Stroop Color-Word Test (SCWT), Symbol Digit Modalities Test (SDMT), Clock Drawing Test (CDT), Rey-Osterrieth complex figure (ROCF), animal fluency test (AFT, naming as many animals as possible in 60 seconds), Boston Naming Test (BNT), and the Trail Making Test (TMT), parts A and B, were also used to evaluate cognitive function. Depression was assessed using the Hamilton Depression Rating Scale 24-Item (HAMD-24).

2.3 Vitamin D measurement

Fasting serum levels of 25-hydroxyvitamin D were quantified, using an electrochemiluminescence immunoassay (Roche Cobas 6000, Tokyo, Japan), according to the manufacturer's instructions.

2.4 MRI data acquisition

All 24 PDND patients were evaluated by magnetic resonance imaging (Achieva, Philips Medical Systems, Best, The Netherlands). MRI scanning was performed with a 3-Tesla MR system. T1-weighted images were collected, using a three-dimensional, magnetization-prepared, rapid-acquisition, gradient-echo sequence. The imaging parameters were as follows: repetition time = 7.1 ms, echo time = 3.5 ms, flip angle = 8°, field of view = 220 × 220 mm, matrix = 352 × 352, slice thickness = 1 mm, 155 continuous slices, and scanning time = 3 minutes and 19 seconds. The clinical assessment on cognition, blood sampling, and MRI were performed on the same day.

2.5 VBM analysis

Using the latest version of SPM12 (Wellcome Department of Imaging Neuroscience, London, United Kingdom), MRIs were segmented into gray matter, white matter, and cerebrospinal fluid images, using a unified tissue segmentation procedure, after image-intensity non-uniformity correction. These segmented gray and white matter images were then spatially normalized against a customized template in the standardized anatomic space, using diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL). The gray and white matter volumes within each voxel were preserved by modulating the images, using the Jacobian determinants derived from spatial normalization by DARTEL, and were then smoothed, using an 8-mm full-width at half maximum (FWHM) Gaussian kernel.

2.6 Statistical analysis.

Data were analyzed using SPSS software, version 23.0. Continuous variables are presented as the mean $\pm$ standard deviation. Comparisons were performed using independent Student's t-tests or chi-square tests, for comparisons between groups. Multiple linear regression analyses were used to analyze the correlations between serum 25-hydroxyvitamin D levels and cognitive function. Multiple regression analyses were performed to explore the associations between 25-hydroxyvitamin D levels and GMV. All analyses were adjusted for intracranial volume, age, sex, education level, UPDRSIII scores, disease duration, BMI, and HAMD scores. All P-values were two-tailed, and a significance level of 0.05 was used.

3. Results

3.1 Clinical and demographic characteristics

The demographic information and clinical features of the forty-eight participants are presented in Table 1. The serum 25-hydroxyvitamin D levels of the PDND group were significantly lower than those of the HC group.

Table 1
Clinical and demographic characteristics of the 48 objectives

	PDND (24)	HC (24)	<i>P</i> -value
Sex, M (%)	12 (50%)	14 (58.33%)	0.562
Age, y	63.1 ± 8.5	65.1 ± 5.9	0.330
Education, y	8.1 ± 3.4	10.1 ± 3.0	0.034*
HBP, n (%)	8 (33.3%)	7 (29.17%)	0.755
DM, n (%)	1 (4.17%)	0	1.000
Smoker, n (%)	5 (20.83%)	5 (20.83%)	1.000
Alcohol intake, n (%)	3 (12.5%)	2 (8.33%)	1.000
BMI, kg/m ²	24.1 ± 2.7	—	—
Disease duration, y	4.2 ± 3.5	—	—
LED, mg	373.8 ± 339.5	—	—
H & Y	2.0 ± 0.7	—	—
UPDRSIII	25.7 ± 10.3	—	—
MMSE	27.2 ± 2.4	28.8 ± 1.3	0.008**
MoCA	22.2 ± 5.4	26.5 ± 2.7	0.001**
HAMD-24	8.4 ± 5.7	3.4 ± 3.7	0.002**
25-hydroxyvitamin D(nmol/L)	41.8 ± 16.0	50.5 ± 9.3	0.027*
Abbreviations: HBP, high blood pressure; DM, diabetes mellitus; BMI, body mass index; LED, L-DOPA equivalent dose; H & Y, Hoehn-Yahr scale; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Rating Scale. BMI is missing in HC.			

3.2 Serum 25-hydroxyvitamin D and cognitive function

As shown in Table 2, after adjusting for age, education level, UPDRSIII scores, and disease duration, the multiple linear regression analyses between serum 25-hydroxyvitamin D levels and the scores of subtests that analyzed cognitive function showed that serum 25-hydroxyvitamin D levels were negatively correlated with TMT-A scores ($P < 0.05$) and positively correlated with SDMT and AVL T scores ($P < 0.05$).

Table 2

Multiple linear regression analyses between serum 25-hydroxyvitamin D levels and cognitive function in PDND patients

	Serum 25-hydroxyvitamin D levels in PDND patients		
	<i>B</i>	<i>T</i>	<i>p</i>
DST (forward)	-0.003	-0.078	0.939
DST (backward)	-0.051	-0.477	0.639
SDMT (90 seconds)	0.367	3.726	0.002**
TMT-A	-1.066	-2.094	0.049*
TMT-B	-0.109	-0.655	0.514
SCWT	-0.021	0.101	0.921
AVLT-H (immediate recall)	0.177	2.845	0.009**
AVLT-H (short-term delayed recall)	0.093	2.791	0.011*
AVLT-H (long-term delayed recall)	0.379	2.052	0.054
AVLT-H (clue recall)	0.095	2.398	0.026*
AVLT-H (recognition)	0.052	2.284	0.035*
ROCF (copy)	0.015	0.129	0.899
ROCF [immediate recall (3 minutes)]	0.237	1.281	0.217
CDT	-0.062	-0.302	0.769
AFT (the first 15 seconds)	-0.008	-0.176	0.864
AFT (the last 45 seconds)	-0.049	-1.032	0.332
BNT (0)	-0.085	-0.466	0.647
BNT (1)	-0.035	-0.725	0.479
BNT (2)	0.040	0.200	0.844
Abbreviations: DST: digit span test; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test; SCWT: Stroop Color-Word Test; AVLT-H: Auditory Verbal Learning Test-Huashan Version; ROCF: Rey-Osterrieth complex figure; CDT: Clock Drawing Test; AFT: animal fluency test; BNT: Boston Naming Test; PDND, Parkinson's disease with non-dementia. ** $P < 0.01$, * $P < 0.05$.			

3.3 Serum 25-hydroxyvitamin D and GMV

As shown in Figure 1, after adjusting for sex, age, education level, UPDRSIII score, disease duration, BMI, HAMD score, and intracranial volume, multiple regression analyses for whole brain GMV and serum 25-hydroxyvitamin D levels showed that the right fusiform gyrus GMV positively correlated with serum 25-hydroxyvitamin D levels (uncorrected $P < 0.001$). The corresponding voxel number, Montreal Neurological Institute (MNI) coordinates, and z-values of the peak point in this region are shown in Table 3.

Table 3
Serum 25-hydroxyvitamin D levels are associated with some brain regions in PDND patients

Active region	side	X	y	Z	Activated voxel	T-value
fusiform gyrus	right	34.5	-51	-15	45	4.015

4. Discussion

Our analyses revealed a significant association between vitamin D, GMV and cognition in PDND patients. The serum 25-hydroxyvitamin D levels of the PDND group were significantly lower than those of the HC group. We also observed that serum 25-hydroxyvitamin D level was negatively correlated with worse performance on some cognitive tests in PDND patients and positively correlated with GMV in right fusiform gyrus. We chose PDND patients, according to the PDD diagnostic criteria established by the International Movement Disorders Association, as our study objects for two reasons. First, it's difficult to finish the complicated cognitive scales in our study for PDD patients. Secondly, magnetic resonance imaging need to stay still for a long time and it's also difficult for PDD patients to finish the examination.

Since Sato et al. first reported that PD patients had lower serum vitamin D levels in 1997, an increasing number of studies have found similar results(15). Evatt et al. found that PD patients had a higher incidence of vitamin D deficiency than healthy controls in their retrospective, cross-sectional study(16). Vitamin D is obtained from the diet and is synthesized in the skin, following exposure to solar ultraviolet B radiation. Kenborg et al. identified 3,819 men with a primary diagnosis of PD and selected 19,282 age- and sex-matched population controls and estimated odds ratios for the development of PD. Among groups divided according to whether they engaged in moderate, frequent, or maximal outdoor work, compared with exclusive indoor work, the result showed that men who work outdoors had a lower risk of developing PD(17). Wang et al. noted that gastrointestinal dysfunction, a frequent non-motor symptom of PD, could impair vitamin absorption and account for these observations. Cognitive impairment often associated with dysphagia, leading to reduced food intake(18).

Numerous studies have demonstrated multiple functions of vitamin D in the nervous system. The functions of vitamin D are mediated through the vitamin D receptor (VDR), which belongs to the nuclear hormone receptor superfamily and acts as a ligand-inducible transcription factor. VDR has been identified in rat and hamster brains and is expressed widely in the adult brain in the temporal(19). Vitamin D appears to have a trophic function in the differentiation and maturation of neurons by controlling the rate of mitosis and the levels of neurotrophins such as the Nerve Growth Factor (NGF) or the neurotrophin 3(20). Vitamin D also promotes neuronal calcium homeostasis by downregulating the expression and

density of calcium channels. Vitamin D also exhibits anti-inflammatory effects in the brain, consistent with reduced inflammatory brain injury following vitamin D repletion(21). Most studies believe that there is a positive correlation between vitamin D deficiency and the cognitive status of the elderly, while some studies believe that there is no correlation between the two(22). Manzo C et al. have further suggested that vitamin D deficiency promotes the development of cognitive impairment in elderly patients with multiple complications(23). In recent years, there have been many studies focusing on the correlation between vitamin D deficiency and the cognitive status of PD. Most studies believe that there is a positive correlation between vitamin D deficiency and the cognitive status of the PD(24–26). In our study, we also observed that lower serum 25-hydroxyvitamin D level was associated with worse performance on some cognitive tests in PDND patients, which was consistent with most researches.

Many studies have described an association between vitamin D, GMV, and brain volume. Gray matter volume (GMV) is a marker of brain atrophy and a potential marker of cognitive function. The intake of vitamin B12, vitamin D, and zinc was positively associated with GMV in patients with normal cognitive function(14). Higher 25-hydroxyvitamin D concentrations were associated with increased concentrations amyloid-beta ($A\beta_{1-42}$) in the cerebral spinal fluid, increased white matter volume, and increased volumetric measures for several brain structures, including structures found in the medial temporal lobe, such as the amygdala and hippocampus, in Alzheimer's disease patients(27). Pauline Ali et al. found that among community-dwelling older adults, lower serum 25OHD concentration was associated with lower GMV in the left calcarine sulcus specifically(28). VBM studies have demonstrated that patients with PD without dementia mainly present atrophy in frontal and temporal areas(29). In our study, we found the precise brain region, that GMV in right fusiform gyrus was positively associated with serum 25-hydroxyvitamin D level in PDND.

The fusiform gyrus participates in a range of visual cognitive functions, such as facial recognition, body part discrimination, and the recognition of various object features. The fusiform gyrus can be subdivided into three distinct subregions, the medial (FGm), lateral (FGl), and anterior (FGa) regions, and their characteristic structural and functional connections have been identified. FGm is primarily positively correlated with the occipital pole and the posterior region of the medial temporal cortex, which comprise the primary visual cortex and the extrastriate cortical areas. Thus, the FGm may be involved in low-level visual processing, interacting with higher-order visual areas and serving as a bridge for the transmission of visual stimuli information. Moreover, studies have found that the bilateral FGm is positively and functionally connected with the auditory network, especially the superior temporal gyrus and the posterior insula(30, 31). The FGl has been widely examined and has been identified to play crucial roles in various visual cognitions, such as face, word, and object recognition(32). Based on whole-brain functional connectivity maps, studies have also found that the FGa was functionally correlated with the bilateral precuneus, posterior cingulate cortex, the rostral part of the middle temporal gyrus, and the middle occipital area. Previous functional MRI studies have revealed that the precuneus, posterior cingulate cortex, and middle temporal gyrus were more active during the resting state and showed decreased activity during the task state. These brain regions are often referred to as the default mode network

(DMN). The functional network connectivity fingerprints also indicated that the FGa was primarily connected with the DMN. Interestingly, the DMN has been found to spatially and functionally overlap with the semantic memory system, and the posterior region of the anterior FG showed high activation associated with semantic cognition(33–35). Our study found that serum 25-hydroxyvitamin D in PDND patients was significantly positively related to Auditory word learning, and we also found that the lower serum 25-hydroxyvitamin D levels, the less GMV in the right fusiform. Combined with the role of fusiform gyrus in cognition, we hypothesized that the low serum 25-hydroxyvitamin D level in PDND patients might affect the auditory word learning ability by reducing the GMV in the right fusiform, leading to the decline of semantic understanding and memory function.

In summary, we found atrophy of the right fusiform gyrus with lower serum 25-hydroxyvitamin D level in PDND patients, and serum 25-hydroxyvitamin D level was closely positive associated with cognition. This finding highlights for the first time that specific brain areas are altered with hypovitaminosis D in PD patients, and help understanding the effects of vitamin D on cognition in PDND patients. Further studies are required to clarify the precise effects of an increased serum 25-hydroxyvitamin D level on cognition.

Our study has several limitations. First, we did not find any association between the whole brain and other cognitive domains, which may be due to the small sample. Second, we should perform similar studies to investigate the correlation between serum 25-hydroxyvitamin D levels, GMV, and cognitive function in PDD patients. Thirdly, because sample size was small and no adjustment for multiple comparisons was made, some of the findings could be due to chance.

Conclusion

We found atrophy of the right fusiform gyrus with lower serum 25-hydroxyvitamin D level in PDND patients, and serum 25-hydroxyvitamin D level was closely positive associated with cognition. We hypothesized that the low serum 25-hydroxyvitamin D level in PDND patients might affect the auditory word learning ability by reducing the GMV in the right fusiform, leading to the decline of semantic understanding and memory function.

Abbreviations

PD, Parkinson's disease; GMV, Gray matter volume; PDND, PD with non-dementia; HC, healthy control; MMSE, Mini-mental state examination; MoCA, Montreal Cognitive Assessment; VBM, voxel-based morphometry; AVLT: Auditory Verbal Learning Test; GMV, gray matter volume; PDD, PD with dementia; LED, L-DOPA equivalent dose; UPDRS, Unified Parkinson's Disease Rating Scale; AVLT-H: Auditory Verbal Learning Test-Huashan Version; DARTEL, diffeomorphic anatomical registration through exponentiated lie algebra; DMN, default mode network.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (JD-LK-2015-109-09), and the participants (or their guardians) have given their written informed consent. We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

Part of the data relates to another article that we are writing, so I don't wish to share the data now. The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to declare

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Authors' contributions

Y.X. and E.W. wrote and reviewed the draft. J.L. and W.L. designed the study. Y.X., J.L., Q.Z. and K.N. collected the data and performed the statistical analysis. All authors read and approved the final manuscript.

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Figures

Figure 1

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