Correlation between Hypovitaminosis D and Nutritional Status with The Severity of Clinical Symptoms And Impaired Cognitive Function in Patients with Parkinson's Disease

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Abstract

Purpose: To evaluate the relationship between the severity of clinical symptoms and cognitive function of patients with Parkinson's disease (PD) and the serum vitamin D level and nutrition status.

Methods: Thirty-three adult PD patient were included in the study (November 2016 to October 2018) and their clinical symptom severity (including the Hoehn and Yahr scale and unified Parkinson's disease rating scale (UPDRS)) and cognitive function (mini-mental state examination) were assessed in two visits (at time of enrollment and one year after the enrollment). In the meanwhile, their renal/liver function, serum level of vitamin D, vitamin B12, Folate and high-sensitive C-reactive protein were also measured for clinical correlation and comparisons.

Results: From the two visits, we found our patients divided into two group, the well-nourished status group and at risk or malnutrition status group. In both visits, we uncovered patients at risk of malnutrition status had worse clinical severity and more impaired memory. As for hypovitaminosis D, the vitamin D level alone made no significant correlation with the clinical severity and cognitive function.

Conclusion: This study revealed that PD patient with at risk of malnutrition status has impaired cognitive function but patients with abnormal serum vitamin D level did not have such influence. But PD patients with abnormal vitamin D level have a higher hs-CRP level which has an influence on the cognitive function of PD patients. Therefore, abnormal serum vitamin D level may have an indirect influence on the cognitive function of PD patients through the influence on the hs-CRP level. This study is limited by the small case-number and short follow-up time. Further large scale study and longer observation period are needed for a better delineation of the relationship between the serum vitamin D level and nutritional status with the clinical condition of the PD patients.

Keywords: Vitamin D deficiency, malnutrition, Parkinson's disease, cognitive impairment, hs-CRP.

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INTRODUCTION

Parkinson's disease (PD) is a common neuro-degenerative disease, especially noted in the elderly[1,2]. The prevalence of PD has increased globally which has leaded to an increasing burden of the society[3]. In Taiwan, the prevalence rate of PD is 147.7 per 10 thousand people in 2011, with an increasing rate of 7.9% per year [4]. PD is a multifactorial disease, and both genetic and environmental factors play a role in its development. Some personal habits including cigarette smoking and caffeine consumption, and environmental heavy metal as well as the use of pesticides and herbicides[5-11] are known to have an influence on the development of PD. Some studies[12-15] show the role of neuroinflammation in the development of PD by increasing microglial and complement activation and the concentration of pro-inflammatory cytokines in the substantia nigra and striatum. Vitamin D has been found to play a role as an anti-inflammatory factor influencing the development and progression of neurodegenerative disease including PD[16-25]. Clinically, many factors are known to have an influence on the serum level of vitamin D including sun exposure, liver function, renal function and state of malabsorption, especially in patients with malnutrition condition[26]. In this study, we evaluated the nutritional states and serum vitamin D levels of 33 PD patients and examined their relationship with the clinical severity and cognitive function by evaluating the clinical score for symptoms severity and the longitudinal cognitive test scores.

MATERIALS AND METHODS

Patient enrollment

We enrolled the patients with a diagnosis of PD from November 2016 to October 2018, in Kaohsiung Chang-Gung Memorial hospital. In this study, patients with PD was diagnosed according to the Queen square UK PD Society Brain Bank clinical diagnostic criteria, with at least one of the following core features including muscular rigidity, 4-6 Hz resting tremor and postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction; then without matching of step 2 exclusive criteria and meeting three or more step 3 supportive prospective criteria of PD[27]. We further confirmed the diagnosis by the finding of ^{99m}Tc-TRODAT-1 SPECT Imaging[28]. Participants were excluded if they had (1) evidence of major territory stroke shown in magnetic resonance (MR) imaging study; (2) metal implantation or other related physical discomforts that avoid MR imaging studies; (3) problems of agitation and/or delirium state relating to medical disorder; (4) alcohol or substance abuse and (5) history of intracranial operation, including thalamotomy, pallidotomy, and/or deep brain stimulation. This study was approved by the hospital Ethics Committee (IRB No. 201600688A3)

Clinical assessment

For each patients, we performed cognitive function test, including mini-mental state examination (MMSE) [29] for cognitive impairment in the first visit. After drop of one dose of levodopa medication, the Hoehn and Yahr (H&Y) scale [30] and unified Parkinson's disease rating scale (UPDRS) for clinical severity of PD[31] were tested before the medication used at noon. The mini-nutrition assessment (MNA)[32] was used for assessing the nutrition status in the first visit of the enrolled patients in which we divided the patients into three groups as well-nourished status, at risk of malnutrition status and malnourished status (well-nourished: ≥24 points, at risk of malnutrition: 17-23.5 points, and malnourished: <17 points). In the follow-up visit (one year after the enrollment), only UPDRS, MNA scores and nutrient status were re-assessed again.

Laboratory definition

The biochemistry data including liver function, renal function, serum levels of vitamin D, folate, and vitamin B12, and inflammatory biomarker (high-sensitive C-reactive protein; hs-CRP) were assessed in the every visit. In this study, the normal value of serum vitamin D level was defined as ≥ 30 ng/ml[33,34]; normal serum value of vitamin B12 was 191-771 pg/mL, and normal serum folate level was 4.6-18.7 ng/mL[35]. In the study, we applied the serum hs-CRP value as a predictor of developing cardiovascular events and the risks were considered to be low, equivocal and high if the hs-CRP values were<1.0, 1.0-3.0 and >3.0, respectively[36,37].

Statistical analysis

After the enrollment, we followed the patients one year after the initial visit. All data were collected for analysis. Clinical and laboratory data were expressed as mean ± standard deviation. The differences between categorical variables and the H&Y scale were constructed using the x2-test; while biomarkers level and score of neurobehavioral assessment by Student's t-test. We analyzed the correlation between the level of serum vitamin D and UPDRS by using the linear regression. All statistical analysis was conducted using SPSS software (SPSS version 22 for Windows®, SPSS Inc., Chicago IL). Statistical significance was set at $p<0.05$.

RESULTS

Initially, we enrolled 47 patients with a diagnosis of PD, but 14 of them dropped from the study because 10 refused further clinical and cognitive assessment and/or the acquirement of laboratory data and the other 4 didn't return the clinics in the second visit. Therefore, only 33 patients completed the whole study course. These 33 enrolled PD patients were 15 men and 18 women aged 56-87 years (mean=71.6 years).

In the initial assessment of nutrition status, none of the 33 enrolled PD patients were scored in the group of malnutrition status; therefore, only the groups of well-nourished status (16) and at risk of malnutrition status (17) were found. Tables 1 and 2 show the comparative results of laboratory data as well as the severity of clinical symptoms and cognitive function between these two groups of PD patients, respectively. Table 1 shows that the UPDRS was higher in the group of at risk of malnutrition status. Although the serum levels of vitamin D were all < 30 ng/ml in both groups of patients, it did not show significant difference between the groups. Table 2 shows that the group of at risk of malnutrition status had a significant impairment in the memory (Trial 1-4 test) and calculation.

In these 33 enrolled PD patients, 23 had a normal serum vitamin D level, while the other 10, a lower vitamin D level. Table 3 shows that the patients with lower serum vitamin D level had a higher hs-CRP level; but the severity of clinical symptoms between the two groups of PD patients did not show significant difference. As to the cognitive state of these two groups of patients, no significant difference was noted (Table 4). For a better analysis of the influence of serum hs-CRP level on the clinical severity and cognitive state of PD patients, Table 5 shows the comparative results of the related items between the PD patients with normal or abnormal hs-CRP level, and only the item "visual objective and space perception (VOSP) score" was significant. The other cognitive domains and the clinical symptom severity of these two

Table 1. The comparison of the laboratory data and cognitive function between the patients with at risk of malnutrition status and well-nourished status in the first visit

	At risk of malnutrition status (N=17)	Well-nourished status (N=16)	p value
Age	71.65±5.58	71.50±11.11	0.962
Gender			
Men	9	6	0.373
Women	8	10	
Clinical score			
H&Y	2.59±1.05	2.28±0.80	0.950
UPDRS	38.24±21.95	25.75±10.21	0.046*
MMSE	22.94±4.18	25.44±3.74	0.081
Laboratory data			
Vitamin D (ng/mL)	27.76±6.77	26.32±6.50	0.538
Vitamin B12 (pg/mL)	784.21±599.70	747.29±344.73	0.831
Folate (ng/mL)	9.96±5.75	13.98±5.10	0.042
hs-CRP (mg/L)	3.91±7.10	3.46±6.44	0.850

UPDRS: unified parkinson's disease rating scale for symptoms severity; H&Y stage: Hoehn&Yah stage; MMSE: mini-mental state examination; hs-CRP: high-sensitive C-reactive protein; *: $p<0.05$

Table 2. The comparison of the cognitive function between the patients with well-nourished status and at risk of malnutrition in the first visit

Neurobehavioral test (full score)	At risk of malnutrition status (N=17)	Well-nourished status (N=16)	p value
MMSE	22.94±4.18	25.44±3.74	0.081
Attention			
Digital forward (9)	7.71±1.26	7.94±1.53	0.637
Memory			
Trial 1-4 test (36)	18.00±4.72	24.06±5.36	0.002*
Trial test 10 minutes recall (9)	4.94±2.16	5.75±1.81	0.254
Recognition of Ray-Osteriieth figure (1)	0.53±0.51	0.63±0.50	0.593
Visual-perceptual-spatial function			
Pentagon (1)	0.71±0.47	0.81±0.40	0.491
Cube (2)	0.47±0.80	0.88±0.89	0.178
Ray-Osteriieth figure (17)	12.82±4.86	13.63±4.33	0.622
Visual object and space perception score (10)	6.53±2.00	7.25±2.46	0.362
Face recognition (6)	3.88±1.36	4.63±1.41	0.134
Executive function			
Digital backward (7)	3.35±1.62	3.81±1.38	0.388
Stroop test	26.35±14.55	24.88±10.86	0.744
Praxis test (8)	7.18±1.07	7.50±0.89	0.356
Alternating patterns (14)	9.47±4.96	11.31±4.44	0.271
Category naming fluency	36.71±10.95	42.25±12.85	0.191
Calculation (5)	3.53±1.23	4.50±0.73	0.010*

MMSE: mini-mental state examination

Table 3. The comparison of clinical symptom severity and laboratory data between the two groups of patients with normal and low serum vitamin D level in the first visit

	Group with abnormal vitamin D level (N=23)	Group with normal vitamin D level (N=10)	p value
Age	71.43±8.53	71.90±9.11	0.892
Gender			
Men	10	5	0.730
Women	13	5	
Nutrition status			
Normal nutrition	12	4	0.520
Risk of malnutrition	11	6	
Clinical score			
UPDRS	28.21±17.69	41.3±16.64	0.058
H&Y stage	2.43±0.99	2.69±0.79	0.413
Laboratory data			
White blood cell count (109/L)	6334.80±1747.36	5330.00±1070.88	0.103
Hemoglobin (gm/dL)	13.50±1.44	12.42±1.51	0.079
Creatinine (mg/dL)	0.94±0.33	0.90±0.27	0.695
ALT (U/L)	19.91±19.61	20.00±19.17	0.991
AST (U/L)	24.52±12.11	23.50±10.58	0.810
Total bilirubin	0.86±0.41	0.74±0.30	0.409
hs-CRP (mg/L)	4.76±7.79	1.26±0.97	0.046*
Folate (ng/mL)	11.19±6.01	13.56±4.91	0.283
Vitamin B12 (pg/mL)	714.03±384.34	886.55±674.20	0.357

UPDRS: unified parkinson's disease rating scale for symptoms severity; H&Y stage: Hoehn&Yah stage; MMSE: mini-mental state examination; ALT: alanine aminotranferease; AST: aspartate aminotransferase; hs-CRP: high sensitivity C-reactive protein; *: $p < 0.05$

Table 4. The comparison of cognitive function between the patients with normal and low serum vitamin D level in the first visit

Neurobehavioral test (full score)	Group with abnormal Vitamin D level (N=23)	Group with normal Vitamin D level (N=10)	p value
MMSE	24.61±3.73	23.10±4.91	0.340
Attention			
Digital forward (9)	8.00±1.28	7.40±1.58	0.257
Memory			
Trial 1-4 test (36)	21.60±6.54	20.65±5.64	0.675
Trial test 10 minutes recall (9)	7.70±4.78	7.20±5.82	0.538
Recognition of Ray-Osteriieth figure (1)	0.65±0.49	0.40±0.52	0.189
Visual-perceptual-spatial function			
Pentagon (1)	0.78±0.42	0.70±0.48	0.624
Cube (2)	0.52±0.73	1.00±1.05	0.215
Ray-Osteriieth figure (17)	13.43±4.19	12.70±5.54	0.677
Visual object and space perception score (10)	6.78±2.37	7.10±1.97	0.714
Face recognition (6)	4.22±1.45	4.30±1.42	0.880
Executive function			
Digital backward (7)	3.74±1.32	3.20±1.87	0.351
Stroop test	25.7±14.30	25.5±14.32	0.968
Praxis test (8)	7.35±1.03	7.3±0.95	0.901
Alternating patterns (14)	10.52±4.68	10.00±5.09	0.436
Category naming fluency	39.35±11.52	39.50±13.87	0.974
Calculation (5)	4.04±1.11	3.90±1.20	0.741

MMSE: mini-mental state examination

Table 5. The comparison of clinical symptom severity and cognitive function between the patients with normal and high hs-CRP level in the first visit

Neurobehavioral test (full score)	Group with abnormal hs-CRP level (N=12)	Group with normal hs-CRP level (N=21)	p value
UPDRS	33.9±20.70	29.17±12.86	0.480
H&Y stage	2.54±0.87	2.38±0.97	0.146
MMSE	24.50±4.38	23.95±4.04	0.719
Attention			
Digital forward (9)	7.92±1.44	7.76±1.38	0.762
Memory			
Trial 1-4 test (36)	20.83±5.92	21.00±5.93	0.939
Trial test 10 minutes recall (9)	5.92±1.62	5.00±2.17	0.213
Recognition of Ray-Osteriieth figure (1)	0.67±0.49	0.52±0.51	0.440
Visual-perceptual-spatial function			
Pentagon (1)	0.92±0.29	0.67±0.48	0.072
Cube (2)	0.58±0.79	0.71±0.90	0.131
Ray-Osteriieth figure (17)	14.83±3.16	12.29±5.03	0.124
Visual object and space perception score (10)	8.00±1.70	9.24±2.28	0.027*
Face recognition (6)	4.67±1.37	4.00±1.41	0.198
Executive function			
Digital backward (7)	3.67±1.50	3.52±1.54	0.797
Stroop test	25.00±7.53	26.00±15.07	0.801
Praxis test (8)	7.17±1.19	7.43±0.87	0.473
Alternating patterns (14)	11.67±4.60	9.62±4.76	0.746
Category naming fluency	38.17±10.43	40.10±13.08	0.665
Calculation (5)	4.08±0.99	3.95±1.20	0.752

hs-CRP: high-sensitivity C-reactive protein; UPDRS: unified Parkinson's disease rating scale for symptoms severity; H&Y stage: Hoehn&Yah stage ; MMSE: mini-mental state examination; *: $p<0.05$

Table 6. The comparison of laboratory data and clinical symptom severity between the patients with normal nutrition status and at risk of malnutrition status in the second visit

	At risk of malnutrition status (N=15)	Well-nourished status (N=18)	p value
Age	72.67±6.70	70.67±9.80	0.513
Gender			
Men	10	5	0.025*
Woman	5	13	
Clinical score			
UPDRS	39.17±16.58	25.42±16.66	0.024*
H&Y stage	2.90±0.85	2.08±0.93	0.086
Laboratory data			
Vitamin D (ng/mL)	27.43±4.15	24.70±6.94	0.192
Vitamin B12 (pg/mL)	880.22±607.54	812.29±535.56	0.735
Folate (ng/mL)	10.61±6.20	12.95±6.99	0.323
hs-CRP (mg/L)	4.94±8.01	2.03±2.54	0.194

UPDRS: unified parkinson's disease rating scale for symptoms severity; H&Y stage: Hoehn&Yah stage; MMSE: mini-mental state examination; hs-CRP: high-sensitive C-reactive protein; *: $p<0.05$

groups of PD patients did not show significant difference.

In the following visit (1 year after the enrollment), we followed the biochemistry data and clinical severity of symptom of the 33 enrolled PD patients. As shown in the Table 6, men had a higher incidence of at risk of malnutrition status and higher severity in clinical symptoms of PD. But with multiple logistic regression analysis, only the scores of clinical symptom severity were significant. There were also no significant difference of clinical severity of clinical symptoms and laboratory data between the groups of with abnormal and normal serum vitamin D levels (Table 7).

DISCUSSION

Because of the increasing medical and insurance burden of PD, it is indispensable for the clinicians to identify the risk factors for the development of severe disability of PD patients. It has been known that neuroinflammation plays a role in the progression of clinical severity in PD[16-18]. Because the important character of vitamin D in the anti-inflammatory process, vitamin D has been reported as an important factor predicting the clinical course of neurodegenerative disorders including PD[19-25]. But in some studies the positive correlation of malnutrition and vitamin D deficiency with the clinical severity of PD has not been confirmed[38,39].

As to the influence of nutritional condition on the general condition of PD and the level of serum vitamin D[26], our study results (Tables 1 and 2) revealed that the PD patients in the group of at risk of malnutrition status had a more severe clinical symptoms and impaired cognitive state (poorer memory and calculation). It is known that there is a high percentage of PD patients at the risk of malnutrition resulting from symptoms of dysphagia, sialorrhea, and constipation[40,42] which may aggravate the motor symptoms causing more complications including depression and cognitive decline. In our study, the patient group with at risk of malnutrition status also had a poor motor performance in the follow-up study (Table 6). In Table 6, we also find that more enrolled male patients became in the group of at risk of malnourished status and this finding is in contrast to the other studies in which they found that the female gender PD patients had a higher risk to become malnutrition[43-45]. This difference may be related to the difference in the social structure and the epidemiology[46].

Table 7. The comparison of clinical symptom severity and laboratory data between the patients with normal and low serum vitamin D level in the second visit

	Group with abnormal Vitamin D level (N=26)	Group with normal Vitamin D level (N=7)	p value
Age	71.88±8.91	70.43±7.64	0.696
Gender			
Men	10	5	0.12
Women	16	2	
Nutrition status			
Normal nutrition	15	3	0.484
Risk of malnutrition	11	4	
Clinical score			
UPDRS	27.58±15.01	46.86±20.13	0.059
H&Y stage	2.29±0.84	3.07±1.24	0.297
Laboratory data			
White blood cell count (109/L)	6334.62±1722.54	6057.14±1669.19	0.706
Hemoglobin (gm/dL)	17.51±23.40	12.87±2.55	0.608
Creatinine (mg/dL)	1.26±1.81	1.10±0.52	0.824
ALT (U/L)	13.63±9.18	22.29±21.33	0.332
AST (U/L)	23.46±5.64	25.71±11.53	0.632
Total bilirubin	0.76±0.36	0.76±0.40	0.978
hs-CRP (mg/L)	2.80±5.08	5.37±8.14	0.308
Folate (ng/mL)	11.59±7.23	12.96±4.06	0.637
Vitamin B12 (pg/mL)	855.40±566.88	797.76±581.50	0.814

UPDRS: unified parkinson's disease rating scale for symptoms severity; H&Y stage: Hoehn&Yah stage; MMSE: mini-mental state examination; ALT: alanine aminotranferease; AST: aspartate aminotransferase; hs-CRP: high sensitivity C-reactive protein; *: $p<0.05$

The prevalence of vitamin D deficiency is estimated to be 5.9%-13% in western countries[47], but its deficiency is known to be much more severe in the Asian, especially the southern Asia people in which severe vitamin D deficiency accounting for 27%-60% of the general population[48,49]. In Taiwan, the prevalence of vitamin D deficiency was reported to be around 22.4%[50]. Therefore, the problem of vitamin D deficiency should not be ignored by the clinicians who are dealing with the treatment of neurodegenerative diseases including PD. As shown in Table 3, about 69.7% (23/33) of the enrolled PD patients had vitamin D deficiency and this figure of incidence is similar to the other reports[24,25,51]. In our study, we did not find the positive correlation between the abnormal serum vitamin D level and the clinical symptom severity (Table 4), but we found that the PD patients with abnormal vitamin D level had a significant higher hs-CRP level (Table 3). Some studies have suggested that vitamin D might act as an anti-inflammatory factor and bring about protective effects against cardiovascular disease by decreasing the circulation hs-CRP level through the suppression of Nuclear factor kappa B (NF-ϰB) and activator of transcription-3 (STAT3) signaling[52-54]. But the level of hs-CRP does not have significant influence on the microglial-related neuroinflammation in PD[55]. This may explain our finding, as shown in Table 5, the serum level of hs-CRP did not influence the clinical symptom severity of PD except the partial cognitive domain (visual-perceptual-spatial function). Therefore, not only the abnormal serum vitamin D level, other mal-nutritional conditions also have a co-contribution to the progression of clinical symptom severity in PD[19-26,38-39,56-67].

Limitation:

First, this study is limited in the sample size. Second, PD is slow progression neurodegenerative disease; therefore, only the one year follow-up designed in this study may not be long enough for a better view to see the related results. Therefore, further large-scale and longer duration study is needed for a better delineation of the relationship of serum vitamin D level and nutritional status of PD with the clinical symptom severity and cognitive state.

CONCLUSION

This study revealed that PD patient with at risk of malnutrition status has impaired cognitive function but patients with abnormal serum vitamin D level did not have such influence. But PD patients with abnormal vitamin D level have a higher hs-CRP level which has an influence on the cognitive function of PD patients. Therefore, abnormal serum vitamin D level may have an indirect influence on the cognitive function of PD patients through the influence on the hs-CRP level. This study is limited by the small case-number and short follow-up time. Further large scale study and longer observation period are needed for a better delineation of the relationship between the serum vitamin D level and nutritional status with the clinical condition of the PD patients.

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