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The effect of hypocalcemia on motor symptoms of Parkinson's disease

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Abstract

Background: The disabling nature of Parkinson's disease (PD) impairs functional mobility and worsens quality of life. Calcium imbalances are thought to have a significant role in the progression of PD.

Objective: To evaluate the relation between calcium deficiency and deterioration of PD motor symptoms.

Methods: A total of 28 idiopathic PD patients were subjected to motor symptoms evaluation using the modified Hoehn–Yahr scale (H–Y), Unified Parkinson's Disease Rating Scale (UPDRS) Part II and III and Schwab and England Activities of Daily Living Scale (S–E ADL). Total and ionized serum calcium levels were measured for the PD patients and the 30 healthy control subjects.

Results: The level of ionized calcium was significantly lower among PD patients (4.19 mg/dl ± 0.53) than in control subjects (4.8 mg/dl ± 0.35) ($p < 0.0001$). The PD patients with hypocalcemia showed marked deterioration of motor symptoms and significant impairment of daily life activities when compared to PD patients with normal calcium levels regarding their scores on the modified H–Y scale ($p = 0.001$), UPDRS-III ($p = 0.001$), UPDRS-II ($p = 0.001$), and S–E ADL scale ($p = 0.001$). Ionized calcium correlated significantly with PD patients' scores on the modified H–Y scale ($p = 0.019$), UPDRS-Part II ($p = 0.001$), UPDRS-Part III ($p = 0.001$) and S–E ADL scale ($p = 0.001$). The significant cutoff point of the ionized calcium for detection of the deteriorated PD patients that presented with stages more than grade 2 of the modified H–Y scale was < 3.99 ($p = 0.037$) with a sensitivity of 80% and specificity of 95%.

Conclusions: Our findings conclude that calcium deficiency could contribute to the deterioration of PD motor symptoms.

Keywords: Parkinson's disease, Calcium, Motor symptoms

Introduction

Parkinson's disease (PD) is ranked among the most disabling neurological disorders globally and is the second most prevailing neurological disease. Parkinson's disease is a complex neurological disorder that leads to the impairment of communication, mobility and the activity of daily life (ADL) [1]. Recently, the incidence of PD has dramatically increased with the aging population expanding [2]. Around 1% of adults over age 60 years and 2.5% of adults over age 70 years suffer from PD [3].

Parkinson's disease's most specific pathological insignia is the deficiency of dopaminergic neurons in the substantia nigra pars compacta and the ensuing depletion of dopamine in the striatum [4]. This deficiency of dopaminergic neurons is the primary cause of motor symptoms of PD. Parkinson's disease is defined by the presence of ubiquitin and Alpha-synuclein (*α-Syn)* positive cytoplasmic inclusion body [5].

Different pathophysiological changes are` involved in the progression of PD, such as mitochondrial dysfunction, oxidative stress, protein aggregation and inflammation [6]. Furthermore, many environmental and genetic risk factors, as well as specific microelements'

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disruption such as calcium and vitamin D have considerable roles in the deterioration of PD [7].

Calcium is an essential mineral that represents the fifth most abundant trace element in the body [8]. Calcium plays an essential role in nerve impulses transmission, muscle contraction, and relaxation. It contributes to several neurometabolic processes, synthesis and secretion of neurotransmitters, as well as oxidation–reduction in the brain parenchyma [9]. In addition, calcium has an essential role in regulation of the cytoplasmic and nuclear calcium signals that stimulate molecular pathways of several transcription factors involved in synaptic plasticity [10].

Pchitskaya et al. [11] reported considerable evidence for a potential association between calcium and onset of neurodegenerative diseases. It is well-known that significant disturbances of serum calcium level, especially hypocalcemia, could contribute to development of different neurological diseases, such as Parkinsonism [12].

This study aimed to evaluate the relation between deficiency of serum calcium levels and the deterioration of motor symptoms of PD patients.

Methods

Study population

This case–control study was carried out in the Neurology Department and Neurology Outpatient Clinic, Zagazig University Hospitals, between the period from July 2018 to October 2020.

A total of 28 idiopathic PD patients who fulfilled the Movement Disorder Society Clinical Diagnostic Criteria for PD were included in this study [13].

Inclusion criteria were PD patients on stages ranging between 1 and 4 on the modified Hoehn–Yahr scale (H–Y) [14], educated PD patients, patients on L-dopa alone or in combination with other drugs and patients with over a year duration of disease.

Exclusion criteria were PD patients with a history of head trauma or cerebrovascular disease, previous history of thyroid and parathyroid dysfunction or medications affecting serum calcium level, patients with hypercalcemia, patients with secondary Parkinsonism features such as supranuclear gaze palsy, dystonia, myoclonus, visual hallucinations, ataxia, orthostatic hypotension, urinary urgency, retention, or significant unexplained erectile dysfunction in men, history of antipsychotics drug intake and intracranial lesion on neuroimaging.

The control subjects constituted 30 healthy volunteers matched to the patients with respect to age, gender, and educational level. They had no history of thyroid, parathyroid, renal disease or drug abuse.

Assessment of motor dysfunction of PD

Detection of the stage of PD was done using modified H–Y scale. It was designed to be a descriptive staging scale to assess the stage of motor impairment. Staging ranges from stage 0 to stage 5.

Evaluation of the severity of PD motor symptoms (during "off" state) based on motor part of Unified Parkinson's Disease Rating Scale (UPDRS) part III [15], which is a rating tool used to evaluate the course of PD and severity of motor symptoms, with a score ranging between 0 and 56.

Assessment of the impairment in activities of daily living was done using the UPDRS part II [15] and Schwab and England Activities of Daily Living Scale (S–E ADL) [16] UPDRS part II evaluates the salivation, speech, handwriting, swallowing, dressing, food cutting, turning in bed, hygiene, freezing, walking, falling, symptomatic complaint of tremor and sensory complaints. Schwab and England Activities of Daily Living is a scale that uses percentages to illustrate the patient's attempt and reliance on the caregivers to perform daily living activities.

Based on the UPDRS III scale, the dominant motor symptoms were defined. The three motor subtypes were: (1) tremor-dominant; (2) akinetic–rigid; and (3) mixed (features of tremor and akinetic–rigid). The ratio of patient's UPDRS III Tremor score; sum of Item 20 (tremor at rest of head, upper and lower extremities) and item 21 (hands' action or postural tremors) divided by 4 to patient's UPDRS akinetic/rigid score; sum of item 22 (rigidity), item 27 (arising from chair) and item 31 (body bradykinesia and hypokinesia) divided by 15, was used to determine dominant motor symptoms. A ratio equal 1 was classified as tremor-dominant, a ratio equal 0.80 was classified as akinetic–rigid, and a ratio between 0.80 and 1.0 was classified as mixed type [17].

Laboratory assessment

Five (ml) fasting blood samples were drawn from all the study participants under septic conditions. It was centrifuged within one hour in the clinical laboratory and analyzed by Cobas 702 automatic analyzer. Any calcium supplements were avoided for 8–12 h before the laboratory test. Provided that plasma protein concentrations are within normal levels, a normal serum calcium level is 8.5–10.5 mg/dl, while a normal ionized calcium level is 4.3–5.3 mg/dl. High serum calcium level or hypercalcemia is defined as a total serum calcium level more than 10.4 mg/dl or an ionized serum calcium level more than 5.2 mg/dl. Hypocalcemia is a total serum calcium level < 8.8 mg/dl or a serum ionized calcium level < 4.7 mg/dl [18].

Administrative and ethical design

A written informed consent was obtained from each participant of this study after explanation of the nature of the study. The protocol of the study was examined and approved by the local ethical committee of the Faculty of Medicine, Zagazig University (#4413 on the fourth of July 2018).

Statistical analysis

The statistical testing was based on Statistical Package for the Social Sciences (SPSS version 20.0) [19]. According to the type of data, Quantitative data were presented as the mean ± SD and the categorical data were presented as a number and percentage. Student *t* test was used to compare the independent groups of normally distributed data. Chi-square test was employed to detect differences among categorical variables. Pearson's *r* correlation was applied to evaluate the correlation strength between variables. A value of $p < 0.05$ was considered as a threshold of significance. Statistical parameters such as sensitivity and specificity, area under receiver operator curve (ROC) and predictive values were also used.

Table 2 Clinical data of PD patients

Clinical data		PD cases $N = 28$ (100%)	
Dominant symptom		No	%
Tremor-dominant		9	32.1%
Akinetic–rigid		9	32.1%
Mixed		10	35.7%
Duration of the disease (years)			
Mean ± SD		7.46 ± 3.24	
Clinical scales		No	%
Modified H–Y	Stage 2	9	32.1%
	Stage 2.5	15	53.6%
	Stage 3	4	14.3%
		Mean ± SD	
UPDRS-III motor		29.32 ± 5.89	
UPDRS-II ADL		29.71 ± 5.82	
S–E ADL scale		68.92 ± 13.42	

SD standard deviation, Modified H–Y scale: modified Hoehn and Yahr scale, UPDRS-III_motor: Unified Parkinson's Disease Rating Scale part III, UPDRS-ADL: Unified Parkinson's Disease Rating Scale Activities of Daily Living part II, S–E ADL scale: Schwab and England Activities of Daily Living Scale

Results

The demographic data of the included PD patients and control subjects are illustrated in Table 1. Between patients and controls, there were no statistically significant differences regarding age ($p = 0.71$), gender ($p = 0.82$), education years ($p = 0.06$) or body mass index (BMI) ($p = 0.16$).

The clinical data of the PD patients in Table 2 showed that there were 9 PD patients (32.1%) presented with tremors as a dominant symptom and 9 (32.1%) presented with akinetic-rigid symptoms and 10 (35.7%) presented with mixed symptoms. The distribution of patients regarding modified H–Y staging was 9 patients (32.1%) in stage 2, 15 patients (53.6%) in stage 2.5 and 4 patients (14.3%) in stage 3. The mean value of the PD patients' scores on UPDRS II was 29.71 ± 5.82, on UPDRS III was 29.32 ± 5.89 and on the S–E ADL scale was 68.92% ± 13.42.

As shown in Table 3, the total and ionized calcium levels were significantly lower in PD patients compared with control subjects. Total calcium was distributed as (8.47 ± 0.89 versus 9.28 ± 0.8, $p < 0.011$) and ionized calcium was distributed as (4.19 ± 0.53 versus 4.8 ± 0.35, $p < 0.001$).

Table 4 illustrates that 12 PD patients (42.85%) had normal calcium levels and 16 PD patients (57.15%) presented

Table 1 Demographic data among PD patients and control subjects

Demographic characteristics	PD patients ($N = 28$)		Control subjects ($N = 30$)		t/X^2	p
	No	%	No	%		
Gender						
Male	14	50%	16	53.3%	0.064	0.82
Female	14	50%	14	46.7%		
Age (years)						
Mean ± SD	59.78 ± 4.41		59.3 ± 5.27		0.38	0.71
Education (years)						
Mean ± SD	12.93 ± 4.45		13.10 ± 3.16		− 1.779	0.06
BMI (kg/m^2)						
Mean ± SD	23.82 ± 2.56		22.8 ± 2.87		1.43	0.16

BMI body mass index, *SD* standard deviation, *t* independent student *t* test, × 2 Chi square, $p < 0.05$ is significant

Table 3 Calcium level distribution between patients and control subjects

Calcium level distribution	PD patients $N=28$ (%)	Control subjects $N=30$ (%)	t	p
Serum calcium (mg/dl)				
Mean ± SD	8.47 ± 0.89	9.28 ± 0.8	3.64	0.001*
Ionized calcium (mg/dl)				
Mean ± SD	4.19 ± 0.53	4.8 ± 0.35	5.21	0.0001*

SD standard deviation, *t* independent student *t* test, $p<0.05$: is significant*

with low calcium levels. The PD patients with hypocalcemia had significant deterioration of motor symptoms compared to PD patients with normal calcium levels as there was a significant difference between them regarding their scores on the modified H–Y scale ($p=0.001$). In addition, the scores of PD patients with low calcium levels were significantly higher than the scores of PD patients with normal calcium levels on UPDRS III scale ($p=0.001$) and UPDRS II ($p=0.003$). The scores of PD patients with hypocalcemia on S–E ADL scale indicated significant impairment of ADL in comparison with scores of PD patients with normal calcium levels ($p=0.001$). There were no significant differences between PD patients with normal and PD patients with low calcium levels regarding the dominant motor symptoms ($p=0.62$).

Total and ionized calcium levels of PD patients with stage 2 of the modified H–Y scale were significantly lower than total and ionized calcium levels of PD patients with stages 2.5 and 3 ($p=0.041$, $p=0.039$, respectively). There were no significant differences between PD patients with stage 2.5 and 3 regarding calcium levels (Table 5).

Table 6 shows that there was a significant cutoff point of total calcium level (less than 8.1 mg/dl) and (less than3.99 mg/dl) for ionized calcium level for detection the deteriorated PD patients that presented in the stages more than grade 2 of modified H–Y scale with sensitivity 80.0% and 80.0%, respectively, and specificity 95% and

Table 4 Comparison between PD patients with normal calcium level and PD patients with hypocalcemia regarding clinical scales

Clinical scales	PD cases $N=28$ (93.33%)				t/X^2	p
	Normocalcemia $N=12$ (42.85%)		Hypocalcemia $N=16$ (57.15%)			
	No	%	No	%		
Dominant symptoms						
Tremor dominant	5	41.7%	4	25.0%	0.96	0.62
Akinetic/rigid	3	25.0%	6	37.5%		
Mixed	4	33.3%	6	37.5%		
Modified H–Y scale						
Stage 2	6	50.0%	3	18.75%	12.393	0.002 *
Stage 2.5	5	41.6%	10	62.5%		
Stage 3	1	8.31%	3	18.75%		
Mean ± SD	2.16 ± 0.24		2.59 ± 0.27		− 3.402	0.001*
UPDRS III (Motor)						
Mean ± SD	25. 91 ± 5.46		32.54 ± 5.12		− 3.223	0.001*
UPDRS II (ADL)						
Mean ± SD	25.75 ± 5.94		32.54 ± 5.12		− 3.590*	0.003*
S–E ADLscale						
Mean ± SD	80.0 ± 8.52		60.62 ± 8.56		5.402	0.001*

SD standard deviation, *t* independent student *t* test, X^2 Chi square test, Modified H–Y scale: modified Hoen and Yahr scale, UPDRS-III_motor: Unified Parkinson's Disease Rating Scale part III, UPDRS–ADL: Unified Parkinson's Disease Rating Scale Activities of Daily Living part II, S–E ADL scale; Schwab and England Activities of Daily Living Scale, $p<0.05$ is significant*

Table 5 Calcium level distribution among different modified H–Y scale

	Modified H–Y stage (2)	Modified H–Y stage (2.5)	Modified H–Y stage (3)	p
Serum calcium	9.31 ± 0.68*	8.09 ± 0.93	7.98 ± 1.61	0.041*
Ionized Calcium	4.71 ± 0.32*	3.96 ± 0.55	3.93 ± 1.12	0.039*

SD standard deviation, $p<0.05$ is *(significant), Modified H–Y modified Hoehn and Yahr scale

Table 6 AUC, cutoff point and validity of calcium level for detection modified H–Y more than stage 2

	AUC	Cutoff point	*p*	95% confidence interval		Sensitivity	Specificity
				Lower bound	Upper bound		
Serum calcium	0.788	< 8.1	0.045*	0.457	1.000	80.0%	95.0%
Ionized calcium	0.800	< 3.99	0.037*	0.441	1.000	80.0%	97.5%

$p < 0.05$ is *(significant) AUC area under curve

Table 7 Correlations between ionized calcium level and PD patients' scores of clinical scales

Clinical scales	Ionized calcium	
	r	*p*
Modified H–Y	− 0.424	0.019*
UPDRS-III Motor	− 0.673	0.001*
UPDRS-II ADL	− 0.725	0.001*
S–E ADL scale	+ 0.7546	0.001*

SD standard deviation, Modified H–Y scale: modified Hoehn and Yahr scale, UPDRS-III_motor: Unified Parkinson's Disease Rating Scale part III, UPDRS-ADL: Unified Parkinson's Disease Rating Scale Activities of Daily Living part II, S–E ADL scale: Schwab and England Activities of Daily Living Scale, *r* correlation coefficient, $p < 0.05$ is significant, * (significant)

97.5% respectively ($p = 0.045$) for total calcium level and ($p = 0.037$) for ionized calcium level.

The results of the present study illustrated that there was a significant association between calcium deficiency and deterioration of motor symptoms, as there were significant negative correlations between ionized calcium levels with modified H–Y scale ($p = 0.019$), UPDRS II patients' scores ($p = 0.001$) and UPDRS III patients scores ($p = 0.001$). Ionized calcium had a significant positive correlation with PD patients' scores on S–E ADL scales ($p = 0.001$) (Table 7).

Discussion

Neurological disorders are the leading source of disability globally, and PD is one of these fast-growing disabling diseases [20]. Variable biochemical markers have fundamental roles in the pathogenesis of PD. Calcium imbalances are proposed to have obvious effects on the progression and deterioration of PD [21].

Our results showed that serum calcium level was significantly lower in PD patients compared with control subjects. These results were in agreement with the results of Meamar et al. [7] and Liu et al. [22] who found a significant decline in serum calcium levels in PD patients. According to Abo- Raya et al. [23], inactivity, rigidity and bradykinesia of PD patients, besides walking difficulties, could reduce sun exposure time, resulting in reducing the synthesis of vitamin D and reduction of calcium absorption. In the context of this topic, Soliman and colleagues [24] found that PD patients had a significantly lower vitamin D level compared to healthy control subjects. Furthermore, Tjaden [25] reported that dopaminergic neuron deficiency in the lower brain stem and cortex could disturb the control and coordination of swallowing in PD patients. Clinical evidence revealed that dysphagia in PD patients could contribute to severe complications, including dehydration, malnutrition, and serum trace elements deficiency, such as calcium [26].

Although there are no significant differences between our PD patients and control subjects regarding age, most of our patients are around 60 years old. Increasing age is considered a great risk factor for decreasing serum calcium and vitamin D levels [27]. The decline of calcium levels in old age has been attributed to reduced 1,25 $(OH)_2$ D synthesis in the kidney and inadequate calcium intake in the elderly [28].

There has been controversy regarding serum calcium levels in PD patients, Sato et al. [29] and Hegde et al. [30] reported a significant increase in serum calcium levels in PD patients. It is proposed that hypercalcemia in PD patients could result from prolonged immobilization with consequently accelerated bone resorption [31].

To the best of our knowledge, few studies evaluated the relationship between serum calcium level disturbances and PD motor symptoms. In this study, we tried to highlight the relation between the calcium deficiency and the severity of motor symptoms of PD using the modified H–Y scale and UPDRS (ADL) and (Motor). We found that PD patients with low serum calcium levels had a significant deterioration of motor symptoms compared to PD patients with normal calcium levels. Our results showed a significant trend showing that when the H–Y stage deteriorated, serum calcium levels became lower. These results were in agreement with Liu et al. [22], who found that serum calcium level was low in PD patients with deteriorated motor symptoms.

Strong evidence suggests that calcium deficiency could contribute to the deterioration of the motor symptoms in PD. Lujan-Martinez et al. [32] reported in their study that it is well-known that PD is characterized by reducing dopaminergic concentration in the nigrostriatal pathway. Calcium has a potent role in neuromuscular stimulation

and neurotransmission. Therefore, calcium deficiency could impair the nerve impulses transmission, which could contribute to partial or total damage of dopaminergic receptors [12]. Indeed, because substantia nigra dopaminergic neurons release dopamine in a calcium activity dependent manner from presynaptic axonal site to the striatum as well as from somatodendritic area to midbrain, so calcium can mediate many physiological functions of substantia nigra dopaminergic neurons [33].

Peterlik and Cross [34] pointed to another link between hypocalcemia and the severity of PD, reporting that low serum calcium level ensues in organ-specific modulation of calcium-sensing receptor activity and initiates an accelerated passage of extracellular Ca^{2+} into a cellular compartment. Therefore, hypocalcemia could promote Ca^{2+} overload in neurons, which contributes to mitochondrial dysfunction, reducing ATP production, generating reactive oxygen species, cytochrome C release, and finally, cell death [33].

The strong relation between hypocalcemia and vitamin D could explain motor symptoms deterioration in PD with low serum calcium levels. Vitamin D increases calcium absorption from the intestines, so that hypocalcemia could result from inadequate vitamin D production and action [35]. Reduced vitamin D level has a remarkable role in the pathogenesis and deterioration of PD [24, 36]. Vitamin D deficiency leads to decreased production of neuron growth factors in substantia nigra, increased level of inflammatory biomarkers, enhancement of oxidation stress, reduction of Neurotrophic factors (NTFs), and deregulation of tyrosine hydroxylase gene expression, consequently dopamine biosynthesis disturbances [37].

The hallmark of hypocalcemia is neuromuscular irritability that can be manifested by fatigue, anxiety, paresthesia of extremities, twitching of facial muscles, muscle sluggishness and frequent muscle cramps. With a significant decrease in serum calcium, action potentials can be formed spontaneously, producing peripheral skeletal muscle contraction [38]. All these pervious clinical symptoms of hypocalcemia could worsen the rigidity and tremors of PD patients.

Conclusions

This study pointed out that calcium deficiency could have a remarkable role in the progression of PD. The results of that study are consistent with the possibility that calcium deficiency could deteriorate motor symptoms and daily living activities of PD patients.

Recommendations

It is of utmost importance to regularly check serum calcium levels in PD patients. It is recommended that PD patients be instructed to increase intake of food known as a good source of calcium and vitamin D and avoid any medication that could alter serum calcium levels.

This study had some limitations, such as the small sample size of the included patients. In addition, we compared the PD patients of hypocalcemia with PD patients with normal calcium level and we did not include PD patients with hypercalcemia in these comparison.

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Author contributions

All the authors carried out this work. ASEE designed the study. MAG collected the patients. EME and AEB conduct analysis and interpretation of the data and write the manuscript. All authors were involved in drafting the article and revising it for important intellectual content and all authors read and approved the final version to be published. All authors read and approved the final manuscript.

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Availability of data and materials

Data supporting the results of this article are included within article.

Declarations

Ethics approval and constant to participate

The study was approved from the Institutional Ethics of the faculty of medicine. Zagazig University (ZU-IRB#4413/7-2018). Written informed consent was obtained from all the participants after explaining the details and benefits as well as risks to them.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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