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ORIGINAL ARTICLE

Assessment of Serum Calcium Level in Relation to Cognitive Dysfunction in Patients with Parkinson's disease.

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Abstract

Introduction; Cognitive impairment is among the most disabling features of Parkinson's disease (PD). Calcium has been postulated to play a role in PD.

Aims; To evaluate the relation between serum calcium disturbances and deterioration of cognitive function in patients with PD.

Methods; A case control study was conducted on 30 patients with clinically definite idiopathic PD diagnosed according to the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease and 30 healthy control subjects. The cognitive function was assessed in the participants using Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) , Rey Auditory verbal learning test (RAVLT) and Visual reproduction subtest of the Wechsler Memory Scale Revised (VR WMS-R).Serum calcium level was measured for all the participants.

Results; The PD patients were found to have a significantly lower level of serum total and ionized calcium than control subjects ($P < 0.05$). The PD patients with hypocalcaemia had a significant impairment of cognitive function in comparison with PD patients with normal calcium level regarding to the scores of both groups in MoCA, RAVLT and VR WMS-R scales ($P = 0.001$ in all parameters) and MMSE ($P = 0.002$) There were significant positive correlations between serum calcium level and PD patients' scores of MoCA, MMSE, RAVLT and VR WMS-R ($P = 0.001$ in all parameters).

Conclusion; The disturbances of serum calcium level especially low serum calcium level could deteriorate cognitive function in PD patients.
Keywords: Parkinson's disease, Calcium, Cognitive function.

INTRODUCTION

Parkinson's disease (PD) is considered the second most common debilitating neurodegenerative disorder characterized by movement dysfunction. It is affecting approximately 1% of the worldwide population older than 65 years. By 2040, it is expected that PD will affect 12 million people **[1]**. In Egypt, the prevalence of PD is higher in Nile valley governorates of Upper Egypt **[2]**.

Parkinson's disease is a hypokinetic movement disorder characterized by a combination of motor symptoms that include bradykinesia, rigidity, tremor and postural instability. In addition, PD is associated with a wide range of non-motor symptoms such as cognitive impairment, autonomic dysfunction, sleep disorders, sensory impairment and neuropsychiatric disorders **[3]**.

It is well apparent in the recent years that non motor symptoms of PD become a major clinical challenge. Cognitive dysfunction is one of the most devastating non-motor symptoms of PD **[4]**. This cognitive impairment could deteriorate social function, impair quality of life, worse the disability and increase caregiver burden and costs of disease related medical care. Statistically, it is one of the most sever symptom of PD that is associated with high mortality **[5]**. The incidence rate of dementia is 100 per 1000 PD patients,

more than 5 times that of age related match controls **[6**].

Calcium is important macronutrient for the central nervous system function as it involved in many neurometabolic processes including oxidation and reduction reactions in brain parenchyma, synthesis and secretion of neurotransmitters **[7].** Therefore previous studies have been pointed to the strong association between calcium and cognitive function **[8,9]**. Serum calcium disturbances have been postulated to play a role in progression of Parkinson's disease **[10].**

The aim of this study is to evaluate the relation between disturbances of serum calcium level and deterioration of cognitive function of PD patients.

METHODS

The present study is a case-control study that included 30 patients with clinically definite idiopathic PD and 30 healthy control subjects .The PD patients were enrolled from Neurology department and Neurology

Outpatient Clinic, Zagazig University Hospitals, in the period from January 2018 to October 2020. The included PD patients fulfilled the criteria for the diagnosis of idiopathic PD based on Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease **[11**].

The control subjects included 30 healthy subjects matched to the patients with respect to age, gender, educational level and socioeconomic state. The following exclusion criteria was applied to both PD patients and control subjects : Illiterate subjects, PD Patients with secondary PD , PD patients on stage 5 of modified H-Y Scale**[12**] , History of head trauma or cerebrovascular disease, History of drug abuse, psychiatric and mental illness, medications affecting serum calcium level, pervious history of thyroid, parathyroid dysfunction and malignant tumors.

Written consent was obtained from all participants after explanation of the procedure. Institutional Review Board, Faculty of medicine Zagazig University approved this study (ZU-IRB#4413/7-2018). The study was done according to the code of Ethics of World Medical Association (Declaration of Helsinki) for the studies involving humans.

All the participants of the study were subjected to the following

EVOLUTION OF PARKINSON'S DISEASE

Assessment the stages of PD was done by using modified Hoehn and Yahr (H-Y) scale **[12]**. Modified H-Y scale was designed to be a descriptive staging scale to assess the stage of motor impairment. The stages range from stage 0 to stage 5 with stage 0 indicates no signs of disease and stage 5 indicates the most severe stage. Stages 4 and 5 as well are referred to as "severe impairment," Stage 3 as "moderate impairment," and other stages were labeled as having "mild impairment**.**

COGNITIVE ASSESSMENT

The global cognitive function of both PD patients and control subjects were evaluated by using Mini-Mental State Examination (MMSE) **[13]**. and Montreal Cognitive Assessment (MoCA) **[14**]. It examines functions including registration, attention, calculation, recall, language, ability to follow simple commands and orientation. Mini-Mental State Examination and MoCA were designed as a rapid screening instrument that assesse different cognitive domains that is including; attention and concentration, language, conceptual thinking, calculations, orientation, executive functions and visuo- constructional skills.

Rey Auditory verbal learning test (RAVLT) **[15]** and Visual reproduction subtest of the Wechsler Memory Scale Revised **[16]** were used as Neuropsychological battery for assessment the verbal and visual memory.

LABORATORY INVESTIGATIONS

Routine investigations which included complete blood picture, liver and kidney functions, lipid profile, and blood sugar level were done to all participants. Assessment of baseline serum albumin level was done to all the participants as hypoalbuminemia is a common cause of false results of hypocalcemia.

Fasting blood samples (5ml) were obtained from all study participants for the measurement of total and ionized calcium. They were advised to avoid calcium supplements for 8-12 hours before testing. It was centrifuged within one hour in the clinical laboratory and analyzed by Cobas702 automatic analyzer. Normal serum calcium level was 8.5-10.5 mg/dl, and normal ionized calcium was 4.3-5.3 mg/dl **[17]**.

STATISTICAL ANALYSIS

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 22) **[18]**. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were

used to test differences for significance;. Difference and association of qualitative variable by Chi square test (X2). Differences between quantitative independent groups by t test, multiple by ANOVA, correlation by Pearson's correlation or Spearman's. P value was set at <0.05 for significant results & <0.001 for high significant result.

RESULTS

The demographic data for included PD patients and control subjects were illustrated in **Table 1**. There were no statistically significant differences between PD patients and control subjects regarding gender (p = 0.606), age ((p = 0.728), education years (p = 0.07), or BMI (p = 0.177).

As regards disease severity H-Y staging scale revealed that most our patients (53.33%) were in stage 2.5 while 30% in stage 2 and 16.67% in stage 3. The mean duration of PD in the patients was 7.36±2.44 years **(Table 2).**

The serum calcium level was distributed as 8.64±1.07 and 9.28±0.81 between PD patients and control subjects respectively and ionized calcium level was distributed as 4.30±0.66 and 4.82±0.35 between PD patients and control subjects respectively. There were significant differences between the patients and control subjects regarding total and ionized calcium level (p <0.011, p <0.001 respectively). Our results showed that there were 12 (40%) PD patients had normal calcium level, 16 (53.37%) PD patients had hypocalcaemia and 2 (6.7%) PD patients had hypercalcaemia **(Table 3).**

The performance of PD patients was worse than control subjects on cognitive function tests, with statistically significant differences between their scores on MoCA (p value =0.001), MMSE (p =0.001), RAVLT (p =0.001) and VR WMS-R (p =0.001) **(Table 4).**

The scores of PD patients with abnormal calcium level on cognitive function tests were significantly lower than the scores of PD patients with normal calcium level on, MoCA (P=0.001), MMSE (P =0.008), RAVLT (P = 0.001) and VR WMS-R (P= 0.001) **(Table 5).**

The PD patients with hypocalcemia showed significant impairment of cognitive function in comparison with PD patients with normal calcium level according to their scores on MoCA (P =0.001), MMSE (P =0.002), RAVLT (P =0.001) and on VR WMS-R (P =0.001) **(Table 6).**

There were highly statistically significant positive correlations between ionized calcium level in PD patients and their scores on MoCA (p = 0.001), MMSE (p = 0.001), RAVLT(p = 0.001), and VR WMS-R (P = 0.001) **(Table 7).**

Table 1: Demographic data of PD patients and control subjects characteristics.

Demographic Characteristics	PD patients (N=30)		Control subjects (N=30)		t/ X^2	P
	No.	%	No.	%		
Gender						
Male	14	46.7%	14	46.7%	0.26	0.606
Female	16	53.3%	16	53.3%		
Age (years) Mean±SD	59.73±4.27		59.3±5.27		0.350	0.728
Education (years) Mean±SD	10.93±4.45		13.10±3.16		-1.779	0.07
BMI (kg/m^2) Mean±SD	22.80±2.87		23.75±2.49		1.367	0.177

BMI =Body Mass Index - SD=Standard deviation - t test =Differences between quantitative independent groups - x2 =Chi square - p< 0.05 is significant.

Table 2: The clinical findings of PD patients

Clinical data	PD cases N=30 (100 %)
Duration of the disease (years)	
Mean±SD	7.36±2.44
Median (Range)	7 (2-14)
Age of disease onset	

Mean±SD		52.37±1.87	
Scale		No	%
Modified H-Y	**Stage 2**	9	30.0%
	Stage 2.5	16	53.33%
	Stage 3	5	16.67 %

SD=Standard deviation - Modified H-Y scale = modified Hoehn and Yahr scale

Table 3: A comparison between PD and control subjects regarding to Calcium level.

Calcium level distribution	**PD patients N =30 (%)**		**control subjects N =30 (%)**	**t/X²**	**P**
Serum calcium (mg/dl) Mean±SD	8.64±1.07		9.28±0.81	-2.629	< 0.011*
Ionized calcium (mg/dl) Mean±SD	4.30±0.66		4.82±0.35	-3.679	< 0.001**
Calcium level	No	%			
Normal Hypocalcaemia Hypercalcaemia	12 16 2	40% 53.37% 6.7%			

SD=Standard deviation - t test= Differences between quantitative independent groups -x2=Chi square test - p< 0.05 is significant - *(significant) - **(highly significant)

Table 4 : A comparison between PD patients and control group regarding to cognitive performance.

Cognitive test	**PD patients N=30**	**Control group N=30**	**t/x2**	**P**
MoCA	19.43±3.61	28.93±1.01	-12.881	0.001**
MMSE	20.33±3.19	28.43±1.27	-8.570	0.001**
RAVLT	9.3±2.07	12.96±1.09	-6.700	0.001**
VR WMS-R	9.43±2.25	12.4±0.89	-2.629	0.001**

SD=Standard deviation - t test =Differences between quantitative independent groups) - X2= Chi square test, MoCA= Montreal Cognitive Assessment, MMSE= Mini-Mental State Examination, RAVLT= Rey Auditory verbal learning test, VR WMS-R= Visual reproduction subtest of the Wechsler Memory Scale Revised, p< 0.05 is significant - * (significant) - **(highly significant)

Table 5: A Comparison between the Cognitive function of PD patients with normocalcemia and PD patients with abnormal calcium level.

Cognitive scales	PD cases N=30		t/X²	P
	Normocalcemia N=12 (40 %)	**Abnormal calcium** N=18 (60%)		
MoCA Mean±SD	22.16±3.27	17.61±2.56	4.266	0.001**
MMSE Mean±SD	22.16±2.62	19.11±3.0	2.864	0.008*
RAVLT Mean±SD	11.08±1.24	8.11±1.60	5.417	0.001**
VR WMS-R Mean±SD	11.58±0.79	8.0±1.68	6.866	0.001**

SD=Standard deviation, t test =Differences between quantitative independent groups) - X2= Chi square test -MoCA= Montreal Cognitive Assessment, MMSE= Mini-Mental State Examination, RAVLT= Rey Auditory verbal learning test, VR WMS-R= Visual reproduction subtest of the Wechsler Memory Scale Revised, p< 0.05 is significant - * (significant) - **(highly significant)

Table 6: A comparison between the cognitive function of PD patients with normocalcemia and those with hypocalcemia.

Cognitive scales	PD cases N=28 (93.33 %)		t/x^2	P
	Normocalcemia (N=12) (42.85%)	**Hypocalcemia** (N=16) (57.15%)		
	Mean±SD	Mean±SD		
MoCA	22.16±3.27	17.12±2.27	4.816	0.001**
MMSE	22.16±2.62	18.56±3.0	3.532	0.002**
RAVLT	11.08±1.24	8.04±1.54	6.987	0.001**
VR WMS-R	11.58±0.79	7.89±1.47	6.965	0.001**

SD=Standard deviation - t test =Differences between quantitative independent groups) -X2= Chi square test -MoCA= Montreal Cognitive Assessment, MMSE= Mini-Mental State Examination, RAVLT= Rey Auditory verbal learning test, VR WMS-R= Visual reproduction subtest of the Wechsler Memory Scale Revised, p< 0.05 is significant - * (significant) - **(highly significant).

Table (7). Correlations between PD patients' ionized calcium levels and their scores on cognitive scales.

cognitive scales	Ionizing Ca R	P
MoCA	+0.776	0.001**
MMSE	+0.809	0.001**
RAVLT	+0.567	0.001**
VR WMS-R	+0.619	0.001**

MoCA= Montreal Cognitive Assessment, MMSE= Mini-Mental State Examination, RAVLT= Rey Auditory verbal learning test, VR WMS-R= Visual reproduction subtest of the Wechsler Memory Scale Revised, r = correlation coefficient, p< 0.05 is significant, * (significant) - **(highly significant).

DISCUSSION

Cognitive dysfunction has a negative effect on the course of PD and contributes substantially to disease burden **[5]**.Although there are strong evidences that countenance the role of calcium disturbances in the deterioration of PD, but there is few data regarding the potential association between serum calcium disturbance and cognitive impairment in PD.

In our study we found that serum calcium level was significantly lower in PD patients compared with control subjects. This result was matching with the results of **Meamar et al.[19]** and **liu et al. [20]** who reported that PD patients had lower serum calcium level in comparison with healthy control subjects. **Abo- Raya et al. [21]** in their study reported that bradykinesia and inactivity of PD patients, beside the difficulties in the walking could reduce the time of sun exposure of these patients which result in reducing synthesis of vitamin D with subsequent reduction of calcium absorption. In addition, loss of dopaminergic neurons in the lower brain stem and cortex could affect the control and the coordination of swallowing in PD patients **[22]**. Dysphagia in PD patients could result in serious health

complications including malnutrition and dehydration. Therefor decrease calcium intake might be the cause of hypocalcemia in the PD patients **[23]**.

On the contrary to the pervious results, **Sato et al**.[**24]**and **Tehrani et al**. **[3]** found significant increasing of the serum calcium level in PD patients. **Sato et al**.**[25]** in their study showed that the hypercalcemia in PD patients could be the results of prolonged immobilization with consequent accelerated bone resorption. In our study we had 2 PD patients with high calcium level and these patients had long standing duration of disease and obvious deteriorated motor symptoms.

Our results declared that control subjects performed better than PD patients on all cognitive function tests. The basis of cognitive dysfunction in PD is the deficits in dopaminergic, cholinergic and noradrenergic systems and the degeneration of nucleus basalis of meynert which is also severely affected in Alzheimer's **[26]**. **Ito et al**.**[27]** reported that reduced fluorodopa uptake in caudate nucleus and frontal lobe cortex of PD patients was correlated with impairment on cognitive tests that evaluate the memory , attention and verbal fluency.

We observed in our study that PD patients with low serum calcium level presented with lower scores on cognitive function tests in comparison with PD patients that had normal serum calcium level. In addition, our results showed that there were significant positive correlation between calcium level and PD patients' scores of cognitive function tests. Our results went side by side to results of **Liu et al**.**[20]** who reported in their study that there was strong association between hypocalcemia and the cognitive impairment in PD patients. **Sato et al**.**[28]** concluded that low serum calcium level is a potentially associated factor for progression of dementia. Another study showed that Alzheimer's patients had lower serum calcium level than non-demented patients **[29]**. **Basheer et al**. **[9]** in their study pointed to the significant relation between cognitive dysfunction and deficiency of calcium and copper in elderly patients.

Gao et al. **[7]** clarified the role of calcium on cognitive function by demonstrating that calcium is involved in different metabolic processes that regulate cognitive function such as synthesis and secretion of neurotransmitters, neurotransmitting function, oxidation- reduction reaction and oxygenation in cerebral parenchyma. **Sutoo and Akiyama [30]** added that increased calcium level stimulates dopamine synthesis in the brain through a calmodulin dependent pathway. It is well apparent that dopamine controls numerous brain functions.

The possible evidence of the link between hypocalcemia and cognitive function impairment is that the patients with low serum calcium level are at a high risk for deterioration of kidney function and glomerular filtration rat (GFR) reduction **[31**].Patients with disturbed kidney function have high risk of carotid atherosclerosis, volume deficits in cerebral white matter regions and consequently poor cognitive performance. Indeed, GFR reduction elevates cystatin C level that could contribute to brain atrophy, white matter lesions, neuronal toxicity and cognitive decline **[32].**

One potentially critical confounding factor regarding serum calcium level is vitamin D. Several studies implied strong relation between cognitive function and vitamin D. As it enhance the synthesis of neurotransmitters including serotonin, acetylcholine esterase, thyroid hormone, nerve growth factors and neurotrophic factors (NTFs) **[33]**. Vitamin D deficiency enhances amyloid- induced apoptosis of neurons, reduces phagocytic clearance of amyloid plaques and elevates level of inflammatory markers in the hippocampus **[34**].

On the other hand, other studies found that high serum calcium level was significantly associated with poor cognitive function **[35,8]**.The putative mechanism linking cognitive dysfunction and high serum calcium level is that the high extracellular calcium level could accelerate calcium entry in neurons leading to calcium overload and consequently compromised synaptic function and eventually neuronal death **[8]**.

However, **Bojarski et al**. **[36]** reported that calcium abnormalities (either hypo or hypercalcemia) are able to enhance dysregulation of neuronal calcium homeostasis. Numerous studies pointed out that normalization of serum calcium disturbances is associated with marked improvement of cognitive dysfunction **[37**,**8, 28]**.

Conclusion

The results of our study revealed that patients of Parkinson's disease have a significantly lower calcium level compared to healthy control subjects. This study pointed out that disturbance of serum calcium level especially low serum calcium level in PD patients could deteriorate cognitive function of those patients. Regarding the results of this study, Patients with PD should be

examined on a regular basis for serum calcium level.

Disclosure of potential conflict of interest

The authors declare that they have no conflict of interest and the study was not support by any source of finding.

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