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ORIGINAL RESEARCH

Assessment of Vitamin B12 and Vitamin D deficiency in patients with Alzheimer's disease and Parkinson's disease

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Abstract

Background: Vitamins are involved in neurogenesis, a defense mechanism working in neurons, metabolic reactions, neuronal survival, and neuronal transmission. Previous studies have implicated role of Vitamin B12 and Vitamin D deficiency in formation of amyloid beta plaques and accumulation of synuclein in patients of Alzheimer's disease and Parkinson's disease. **Aims:** We conducted this study to estimate the deficiency of vitamin D and vitamin B_{12} in patients of Alzheimer's disease and Parkinson's disease and assess their clinical correlation. **Methods:** 83 patients of Parkinson's disease and Alzheimer's disease were recruited in the study as per a predefined inclusion criteria. Vitamin B12 and Vitamin D levels were tested in all patients included in the study. **Results:** 70 % patients of Alzheimer's disease and 75% patients of Parkinson's disease were found to have low levels of vitamin D; with significant correlation with the severity of dementia. Vitamin B12 deficiency was seen in 23.5% patients of Alzheimer's disease and 20.4% patients with Parkinson's disease. The severity of Vitamin B12 deficiency correlated significantly with severity of dementia in Parkinson's disease. **Conclusion:** Vitamin B12 and Vitamin D deficiency exists in patients with Alzheimer's disease and Parkinson's disease with linear correlation with the severity of dementia in these patients.

Key words: Parkinson's disease, Alzheimer's disease, Vitamin D, Vitamin B12, Neurodegenerative Diseases

Introduction

Neurodegenerative diseases (NDDs) are traditionally defined as disorders with selective loss of neurons and distinct involvement of functional systems defining clinical presentation. Recent studies have demonstrated that proteins with altered physiochemical properties get deposited in the neurons and glial cells in neurodegenerative diseases. Various diseases that come under the spectrum of NDD are Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD) and PD-related disorders, Multi-system atrophy, Prion diseases, Motor neuron disease (MND), Huntington's disease (HD), Spinocerebellar ataxia (SCA) and Spinal muscular atrophy (SMA)(1).

The Parkinson's disease is a major cause of disability in the elderly. Clinically, it is characterized by tremor, rigidity, slowness of movement, and postural imbalance. Its risk factors are relatively unknown. However, both biological plausibility and epidemiological data indicate that vitamin D

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deficiency may contribute to its development(2). Vitamin D is obtained from diet and is photo-synthesized in the skin by the action of solar Ultraviolet-B radiation. The vitamin D receptors and 1,25 dihydroxy vitamin D have been found in high levels in the substantia nigra, the region of the brain affected most by Parkinson's disease(3). This raises the possibility that chronic inadequacy of vitamin D leads to the loss of dopaminergic neurons in the substantia nigra region and further Parkinson's disease. Oxidative stress has been suggested to contribute to the pathogenesis of PD(4). Alzheimer's disease (AD) has been associated with up-regulation of pro-inflammatory cytokines (e.g., specific gene variants for TNF-α; IL-6; IFN-γ) and low plasma levels of cyanocobalamin (vitamin B12). Several studies have shown that low cyanocobalamin status or a raised total homocysteine—a common finding in cobalamin deficiency is associated with an increased risk of Alzheimer's disease(5). Hence, the deficiencies of both vitamin D and vitamin B-12 appear to play a role in neurodegenerative diseases. Be it their neuroprotective effect, or reducing oxidative stress, these vitamins seem to be protective. Both water- and lipid-soluble vitamins prevent Parkinson's and Alzheimer's disease in a substantial manner. As their deficiency is fairly common in the elderly population, replacement of these can lead to major breakthrough in the management of NDD if a definite link is established regarding their preventive role.

We conducted this study to assess the levels of Vitamin D and Vitamin B12 in patients of two most common neurodegenerative disorders encountered in clinical practice, Alzheimer's disease and Parkinson's disease.

Aims and objectives

The current study was aimed to study the prevalence of Vitamin B12 and Vitamin D deficiency in patients with Alzheimer's disease and Parkinson's disease and assess their correlation with the severity of disease.

Material and methods

This study was carried out in the Department of Medicine, Sarojini Naidu Medical College, Agra over a period of one and a half years. A total of 83 patients of Parkinson's disease and Alzheimer's disease attending the Neurology OPD and admitted indoor were recruited in the study. This study was approved by Institutional Ethics Committee and written informed consent was obtained from all participants before inclusion in the study.

Inclusion criteria

1. Patients of Parkinson's disease and Alzheimer's disease who gave written informed consent.

Exclusion criteria

1. Patients taking multivitamin or vitamin B complex supplements.
2. Patients with other conditions predisposing for vitamin B12 deficiency.
3. Patients with other conditions predisposing for vitamin D deficiency.
4. Patients with any intracranial space occupying lesion.

Detailed history, physical examination and neurological examination were carried out in all patients as per a predesigned proforma. The total scores of Mini Mental State Examination (MMSE) and Dementia Severity Rating Scale (DSRS) were calculated for all patients. Hemogram and biochemistry investigations including blood sugar levels, liver and renal function tests, serum Vitamin D3 (25-Hydroxy) and serum Vitamin B12 levels were done.

Statistical analysis

The statistical analysis was carried out using Statistical Package for Social Sciences 23.0 for windows. The demographic data was presented using the measures of central location including mean, median, range, etc. Comparison between discrete variables was done by Chi square test, while continuous variables were compared using Non parametric tests such as Mann Whitney test. P value of ≤ 0.05 was considered as statistically significant.

Results

Total 83 patients of neurodegenerative disorder were studied, out of which 49 (59%) were of Parkinson disease and 34 (41%) of Alzheimer's disease. Maximum patients of Parkinson disease

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(51%) were between 61-70 year of age group, followed by 71-80 years of age (34.6%). In case of Alzheimer's disease, most of the patients were in age group 71-80 (48.7%) followed by age group 61-70 years (29.4%). Out of 34 patients of Alzheimer's disease, 18 (52.9%) were females and 16 (47%) were males and in Parkinson's disease out of 49 patients, 22 (44.9%) were females and 27 (55.1%) were males. MMSE scoring was done in all patients and dementia was further graded as mild (MMSE 18-23), moderate (MMSE 10-17) and severe dementia (MMSE <10). Among the patients with Alzheimer's disease, 12 (35.3%) had normal MMSE, 6 (17.64%) had mild dementia, 8 (23.5%) had moderate dementia and 8 (23.5%) had severe dementia. In patients with Parkinson's disease, 15 (30.6%) had normal MMSE, 12 (24.5%) had mild dementia, 14 (28.57%) had moderate dementia and 8 (16.3%) had severe dementia.

Dementia severity rating scale (DSRS) was also applied to all patients and dementia scoring was graded into mild (DSRS 0-18), moderate (DSRS 19-36) and severe dementia (DSRS 37-54). In patients with Alzheimer's disease, 12 patients each (35.3%) had mild and moderate dementia while 10 (29.5%) had severe dementia. 34 patients (69.4%) of Parkinson's disease had mild dementia according to DSRS, while 8 (16.3%) had moderate and 7 (14.3%) had severe dementia.

Vitamin D3 and Vitamin B12 levels were tested in all patients. Vitamin D deficiency was seen in 24 patients (70.5%) of Alzheimer's disease, 5 (20.8%) had severe Vitamin D deficiency. In patients with Parkinson's disease, 37 (75.5%) patients had Vitamin D deficiency and 10 (27%) were severely deficient. Vitamin B12 deficiency was seen in 8 patients (23.5%) of Alzheimer's disease and 10 (20.4%) of patients with Parkinson's disease, out of which 4 (40%) were severely deficient.

We compared the levels of Vitamin D and Vitamin B12 with the severity of dementia in patients with Alzheimer's disease and Parkinson's disease. Interestingly, the patients who had severe dementia were more deficient in Vitamin D levels as compared to those with normal MMSE and the results were statistically significant ($p<0.01$). The severity of Vitamin B12 deficiency had significant association with severity of dementia in Parkinson's disease, but the results were non-significant in patients with Alzheimer's disease. All patients with Vitamin B12 and Vitamin D deficiency were treated according to the standard treatment protocols.

Table 1 : Demographic profile of cases

Age (in Years)	AD (n=34)/percentage	PD (n=49)/percentage	Total (n=83)
< 60	0(0)	5(10.2)	5
61 – 70	10(29.4)	25(51.02)	35
71 – 80	20(58.8)	17(34.7)	37
> 80	4(11.76)	2(4.08)	6
Gender distribution			
Females	18 (52.9)	22 (44.9)	40
Males	16 (47)	27 (55.1)	43

Table 2 : Dementia severity scores of cases in study

MMSE Level	AD (n=34)/percentage	PD (n=49)/percentage	Total	P value
Normal (24-30)	12(44.44)	15(55.56)	27	$\chi2 = 1.30$ $p = 0.73$
Mild (18 - 23)	6(33.33)	12(66.67)	18	
Moderate (10 - 17)	8(36.36)	14(63.64)	22	
Severe (< 10)	8(50.0)	8(50.0)	16	
DSRS Scale	**AD (n=34)/percentage**	**PD (n=49)/percentage**	**Total**	**P value**
Mild (0 - 18)	12 (35.29)	34 (69.38)	46	$\chi2 = 9.44$ $p = 0.009$
Moderate (19 - 36)	12 (35.29)	8 (16.32)	20	
Severe (37 - 54)	10 (29.41)	7 (14.28)	17	

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Table 3: Distribution of cases according to Vitamin D and Vitamin B 12 deficiency

Vitamin D levels	AD (n=34)	PD (n=49)	Total (n=83)	p Value
Normal (> 30)	10(45.45)	12(54.55)	22	
Insufficient (21 - 30)	9(39.13)	14(60.87)	23	$\chi 2 = 0.63$ $p = 0.88$
Deficient (11-20)	10(43.48)	13(56.52)	23	
Severely Deficient (< 10)	5(33.33)	10(66.67)	15	
Vitamin B 12 levels	**AD**	**PD**	**Total**	**p Value**
Normal (200 - 1000)	26(40.0)	39(60.0)	65	$\chi 2 = 4.31$ $p = 0.12$
Mild (100 - 200)	8(57.14)	6(42.86)	14	
Severe (< 100)	0(0.0)	4(100.0)	4	

Table 4 : Association of MMSE level with Vitamin D deficiency in AD and PD:

Disease Level	Vitamin D level	MMSE Level				Total	P value
		Normal	Mild	Moderate	Severe		
AD	**Normal**	10(100.0)	0	0	0	**10**	$\chi 2 = 64.03$ $p = 0.0001$
	Insufficient	2(22.22)	6(66.67)	1(11.11)	0	**9**	
	Deficient	0	0	7(70.0)	3(30.0)	**10**	
	Severely Deficient	0	0	0	5(100.0)	**5**	
	Total	**12**	**6**	**8**	**8**	**34**	
PD	**Normal**	12(100.0)	0	0	0	**12**	$\chi 2 = 107.0$ $p = < 0.0001$
	Insufficient	3(21.43)	11(78.57)	0	0	**14**	
	Deficient	0	1(7.69)	12(92.31)	0	**13**	
	Severely Deficient	0	0	2(20.0)	8(80.0)	**10**	
	Total	**15**	**12**	**14**	**8**	**49**	

Discussion

In our study, a total of 83 patients of neurodegenerative diseases were included, out of which 34 (40.9%) had Alzheimer's disease and 49 (59%) had Parkinson's disease. Majority of patients in our study had Vitamin D deficiency (70% patients of Alzheimer's disease and 75.5% patients with Parkinson's disease). The results are consistent with a study by Littlejohns et al which showed that majority of the patients of Neurodegenerative Diseases (approximately 74%) have low level of vitamin D(6). They also found a strong association between baseline vitamin D concentrations and the risk of incident all-cause dementia and AD. The pathophysiological mechanisms implicated have been demonstrated by various in vitro and in vivo studies (7). The amyloid plaques, along with neurofibrillary tangles, represent features of AD, it has been shown that $1,25(OH)_2D$ can help the amyloid plaques phagocytosis and clearance by the innate immune cells, hence Vitamin D can prevent as well as slow the progression of Alzheimer's disease. Also Vitamin D plays a role in reducing cerebral microenvironment inflammation and oxidative stress, which are regarded as possible mechanisms underlying neurodegeneration(8).(bivona) It has also been suggested in a study by Newmark et al, that the Vitamin D receptor and 1α-hydroxylase, the enzyme that converts vitamin D to its active form, are highly expressed in the substantia nigra, and inadequate levels of circulating vitamin D may lead to dysfunction or cell death within the substantia nigra, resulting in Parkinson's disease(2).

In our study, we also assessed the correlation between deficient Vitamin D levels and severity of dementia on MMSE scale and DSRS scale. It was observed that the patients with normal levels of vitamin D had normal MMSE score and mild to moderate dementia on DSRS scale. However the patients with severely deficient Vitamin D levels had moderate to severe dementia on both the scoring

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systems. These results were consistent with a previous meta-analysis done by Balion etal, which showed that individuals with AD had lower Vitamin D concentrations compared to those without AD, and Mini Mental State Examination scores were lower in individuals with lower Vitamin D concentrations(9).

In our study, 23.5% of patients with Alzheimer's disease and 20% of patients with Parkinson's disease had Vitamin B12 deficiency. The deficient levels of Vitamin B12 did not correlate with severity of dementia in Alzheimer's disease, however, however, all 4 patients of Parkinson's disease with severe deficiency of Vitamin B12 levels were found to have severe dementia on MMSE and DSRS scoring. Elevated methylmalonic acid and serum homocysteine levels are specific markers of vitamin B12 deficiency, and are also associated with poor myelination. Elevated homocysteine levels may be associated with Alzheimer's disease, cardiovascular disease, and stroke. Low vitamin B12 and high homocysteine levels may also cause silent brain injury through oxidative stress, resulting in calcium influx and apoptosis (Jatoi et al(10)). In PD particularly, lower B12 levels might be more likely to develop for a number of reasons, including change in dietary intake of B12 (some adopt a low-protein diet), *Helicobacter pylori* infection, delayed gastric emptying and development of constipation, which is associated with bacterial overgrowth. A review by Moore et al observed that Vitamin B12 deficiency is associated with cognitive impairment in patients with Alzheimer's disease, vascular dementia, and Parkinson's disease(11). Vitamin B12 supplements administered orally or parenterally at high dose (1 mg daily) were effective in correcting biochemical deficiency, but improved cognition only in patients with pre-existing vitamin B12 deficiency. Similar results were seen in DATATOP study where among untreated Parkinson's disease (PD) patients, 5% had deficient Vitamin B12 levels (< 212 pg/ml) and 13% had borderline low level (< 250 pg/ml). The participants in the lowest B12 tertile had greater annual worsening of gait and balance compared to those in the middle or upper B12 tertiles(12).

Conclusion

We found a clear association between low vitamin D and Vitamin B12 levels and cognitive impairment in Alzheimer's disease and Parkinson's disease with a linear correlation with the severity of dementia. Therefore, further studies are needed to confirm and refine the observed associations over a larger scale and to determine whether this change will translate to a reduction in cognitive decline.

Moreover, we favour the screening for vitamin D and vitamin B12 deficiency in the elderly population, to find and prevent the possible causes of this deficiency state, as this can be an easily preventable cause of impending dementia before the cognitive decline becomes irreversible.

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