

## Original Research Article

# Study of the prevalence of isolated vitamin B12 deficiency related dementia in patients presenting to a tertiary care hospital

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## ABSTRACT

**Background:** Objective of the study was to determine the prevalence of Isolated B12 deficient dementia in patients presenting to a tertiary care hospital. The MMSE was much lower in B12 deficiency compared to irreversible causes. Thus, shorter duration, severe dementia, focal neurological signs, and a vegetarian diet were significantly associated with the development of B12 deficiency.

**Methods:** Based on exclusion and inclusion criteria 100 patients were included in this study, a detailed history of the patient were taken with respect to duration of dementia and its symptoms, type and treatment. Study in terms of the correlation of the clinical features with investigations and diet. Estimation of the prevalence of dementia with reference to B12 deficiency. Mean MMSE analysis, assessment of the improvement in MMSE after treatment with B12 injections after a 6-8 wks period.

**Results:** In this study most of our patients were in the 60-69 age groups across all causes of dementia, 22 out of 26, B12 deficient patients were vegetarians. This value was in keeping with the known fact that a vegetarian diet predisposes a person to develop B12 deficiency. The association between B12 deficiency, high MCV and megaloblastic blood picture in peripheral blood smear was significant. The MMSE scores were significantly lower 13.42 in patients with B12 deficiency as compared to those with Alzheimer's 14.3 means and those with multi-infarct state 17.3 means.

**Conclusions:** The duration of the presentation in B12 deficiency was 10-12 months averagely. There was a significant improvement in MMSE after treatment in pure B12 deficient patients (by 9 points) if they presented within one year of symptoms. Except for myelopathy, there was an improvement in other neurological symptoms and signs. Early diagnosis and proper treatment can make improvements in a patient's memory and quality of life.

**Keywords:** Dementia, Diet, Mean corpuscular volume, Mini-Mental State Exam score, Vitamin B12 deficiency

## INTRODUCTION

Dementia, by definition, is an acquired impairment of memory, intellectual functioning, and which is not associated with fluctuations in the level of consciousness.<sup>1</sup> Dementia is a frequent problem in the elderly above 50 years, with the prevalence increasing with age. It is one major cause of morbidity in the elderly. In that vitamin B12 deficiency is the treatable

one. It can cause isolated dementia and that it can be a coexisting factor in other irreversible dementias. The prevalence of dementia increases to twice in every five years of life after the age of 65 worldwide. The total number of people with dementia in the world was 11 million in 1980, 18 million in 2000, and is likely to be 34 million in 2025.<sup>2</sup> The data for B12 lack and elderly patients with dementia seems to be limited to a handful of studies in India. B12 deficiency is more common in

North India.<sup>3</sup> The first significant study which looked into various causes of dementia in the elderly (>60yrs) in India was from SGPGI hospital.<sup>4</sup> In India, the percentage of people above 60 years of age was 5.9 and 7.2 in 1970 and 1995, respectively, expected to rise to 11% by 2020.<sup>5</sup>

Mild, and usually subclinical cobalamin deficiency appears to occur (or be recognized) with increased frequency (10 to 24%) in the elderly.<sup>6</sup> In a population-based cross-sectional analysis in the UK prevalence was approximately 5 and 10% in those age 65 to 74 and those more than 75 years of age, respectively, and the majority of them had dementia.<sup>7,8</sup> That's why this study was done on the prevalence of vitamin B12 dementia in the older adults presenting to a tertiary care hospital in Konaseema and looking at the prevalence of B12 deficiency and analyzing the profile of B12 deficient patients.

## METHODS

The study conducted in Konaseema Institute of Medical Sciences Amalapuram, an 800 bedded Tertiary care hospital, Eligible subjects recruited from the departments of medicine, neurology. A prospective cohort study that involving 100 elderly patients with dementia.

### Inclusion criteria

- Elderly patients more than 60 years of age, who were literate and had
- Dementia as per MMSE (English & Telugu versions < 24).

### Exclusion criteria

- Delirium presentation.
- Recent vitamin B12 injections or chronic vitamin users.
- Recent history of blood transfusions.
- Constant bed-ridden, malnourished multi-infarct dementias.

This study was a prospective cohort study done between June 2018 and April 2019. All patients who presented to OPD and IPD with complaints of dementia (satisfying the inclusion criteria) were included in the study and evaluated further with detailed history, examination, and MMSE. Subsequently, the patient's other investigations that included complete hemogram, peripheral blood smear, MCV, TSH, HIV ELISA, VDRL, B12 and folate levels, and neuroimaging when indicated. B12 and folate levels were done by biochemistry lab twice a month.

By definition, severe B12 deficiency diagnosed when the B12 levels were less than 150 pmol/L based on our lab's colorimetric assay. A level of 150-200 would indicate mild lack, and above 200 was considered normal. In our analysis, we have included only severe B12 deficiency (<150 pmol/L). The standard B12 schedule followed, starting with a daily intramuscular injection of B12

1000mcg for a week, followed by once a week for one month and then to continue once a month. The patients asked to come back for follow up after 6-8 wks of treatment for a repeat MMSE.

### Data analysis

- Analysis of the prevalence of various dementias in the elderly population presenting to our hospital.
- Estimation of the prevalence of reversible causes of dementia with particular reference to B12 deficiency.
- Severe B12 lack would be further classified as isolated B12 deficiency or associated with other irreversible causes like Alzheimer's or multi infarct state.
- The profile of B12 deficient patients study concerning their clinical presentation, lab parameters, and dietary habits.
- Mean MMSE analysis, including subgroup analysis.
- Assessment of the improvement in MMSE after treatment with B12 injections after 6-8 wks period.

### Statistical analysis

Descriptive statistics calculated using SPSS software. A chi-square test used for comparison of categorical variables. A 'p' value less than 0.05 was considered statistically significant. All reported p values are two-sided.

## RESULTS

The age and sex distribution of the study population is shown in Table 1. All patients were more than 60 years of age, with the maximum being in the 60-70 year age category (70%). Only 6 percent were older than 80 years; most of our patients were in the 60-69 age groups across all causes of dementia. Thus, no increasing trend was noticeable between the various groups. Between 60 to 69 year age group 10 patients have Alzheimer disease, 30 patients have multi infarct and 20 have vitamin b 12 deficiency. Between 70 to 79 year of age 6 patients have Alzheimer's disease, 11 have multi infarct and 5 have vitamin B12 deficiency.

As per Table 2, the average duration of dementia across all categories was 38.01 months. By comparison with the final diagnosis, it found that the duration for Alzheimer's was the longest (76 months) followed by mixed state (56 months) followed by MID (46 months), followed by B12 deficiency (16 months). Mean duration of dementia in Alzheimer's group was 40.81±3.48 months. Mean duration of dementia in Multi infarct disease group was 60.47±8.81 months. Mean duration of dementia in Isolated B12 deficiency group was 11.6±1.49 months.

As per Table 3, the symptoms of parenthesis, anorexia, hyper pigmentation, imbalance, vision problems were significantly more common in B12 deficiency group

whereas difficulty in walking and muscle weakness was significantly common more in the vascular/multi-infarct dementia group. Paralysis was present in 17% patients, anorexia was present in 19% patients, and hyperpigmentation was present in 19% patients. Muscle

weakness and imbalance was most common which was 35 and 53 respectively. Paresthesia, anorexia and imbalance were common in vitamin deficiency group which was present in 10, 15, and 11 patients respectively.

**Table 1: Age distribution of the study population.**

Age	Total Frequency (sex:males+females)	Alzheimer's	Multi infarct	B12 DEF	Mixed
60-69	71 (51+20)	10	30	20	11
70-79	23(15+8)	6	11	5	1
>80	6(4+2)	1	3	1	1
Total	100(70+30)	17	44	26	13

**Table 2: Duration of dementia.**

Duration of dementia (in months)	All patients	Alzheimer's	Multi infarct disease	Isolated B12 deficiency	Mixed B12 deficiency
Mean±SD	38.01.2±17.7	60.47±8.81	40.81±3.48	11.6±1.49	51.8±1.72
Minimum	9	48	36	9	48
Maximum	76	76	46	16	56

**Table 3: Frequency of clinical features (symptoms).**

Complaint	Alzheimer's	Multi infarct	B12def	Mixed	Total %
Paresthesia	1	2	10	4	17
Anorexia	1	2	15	1	19
Hyperpigmentation	0	1	5	1	7
Muscle weakness	1	21	4	9	35
Imbalance	3	26	11	13	53
Eye problems	1	2	7	1	11
Psychiatric	7	1	3	1	12

**Table 4: Frequency of clinical features (sign).**

Sign	Freq	Alzheimer's	Multi infarct	B12 DEF	Mixed
Pallor	37	4	6	23	4
Glossitis	15	0	1	12	2
Pedal Edema	6	1	3	1	1
Optic neuropathy	11	1	1	8	1
Peripheral neuropathy	35	3	3	23	6
Myelopathy	18	1	2	11	4
Ataxia	16	1	2	10	3
Hemiplegic	34	1	31	0	2
Cerebellar signs	7	0	5	2	0

The most common finding during the examination was hemiplegic, followed by Peripheral neuropathy and myelopathy. The features of glossitis, optic neuritis, neuropathy, ataxia, and myelopathy were significantly more in B12 deficient group, whereas stroke signs were much more in the vascular dementia group. Pallor was present in 37 patients out of that 23 have vitamin B 12 deficiencies. Peripheral neuropathy was present in 11 patients out of that 23 have vitamin B 23 deficiencies.

Myelopathy was present in 11 patients out of that 23 have vitamin B 11 deficiencies (Table 4).

As per Table 5 the most frequent cause of dementia in our study was the two irreversible causes (Alzheimer's and multi-infarct) accounting for more than 50% of the study population. The third most common cause was isolated vitamin B12 deficiency, which was the commonest cause among the reversible dementias. Multi

infarct dementia was present in 32 patients, Alzheimer’s disease was present in 24 patients but vitamin B 12 deficiency was present in 20 patients.

**Table 5: Final diagnosis.**

Final diagnosis	Frequency
Alzheimer's	24
Multi Infarct dementia	36
B12 deficiency	20
Diffuse Lewy body dementia	2
Normal Pressure Hydrocephalus	1
Parkinsonism with dementia	3
B12 and Alzheimer	1
B12 and multi infarct disease	5
Alcohol-related	4
Chronic meningitis with sequelae	2
Depression	1
Miscellaneous	1
Total	100

**Table 7: Correlation between peripheral blood smear and B12 deficiency: (p<0.001).**

Peripheral blood smear	Normal	Hypochromic microcytic	Megaloblastic	Dimorphic	Total
B12 normal	57	13	1	3	74
B12 deficient	3	2	18	3	26
Total	60	15	19	6	100

**Table 8: MCV and B12 deficiency.**

	B12 Normal	B12 Deficient	Mean of MCV and SD	Total
MCV	High	21	100.4±8.8	24
	Normal/Low	5	85.2±5.4	76
Total	74	26		100

Table 7 shows, 18 patients out of 26 had a megaloblastic blood picture, with hyper segmented neutrophils, basophilic stippling, ovalocytes, and macro ovalocytes. The association between B12 deficiency and megaloblastic blood picture was significant (p<0.001). Three patients had a normal blood picture though their B12 levels were deficient. And three patients had a dimorphic blood picture with both megaloblastic and microcytic changes. Only two patients had hypochromic and microcytic blood picture despite low B12 levels.

**Correlation between MCV and B12 deficiency (p <0.001)**

As seen in Table 8, there was a significant correlation between high MCV and B12 deficiencies. The average MCV was 100.4 in B12 deficient patients and 85.2 in others. It is interesting to note that five patients had an average/low MCV with low B12 levels.

**Association of diet with B12 deficiency: p <0.001**

Table 6 shows, there was a significant correlation between vegetarian diet and B12 deficiency when compared to the rest of the study patients (p<0.001). 22 out of 26, B12 deficient patients were vegetarians. This value was in keeping with the known fact that a vegetarian diet predisposes a person to develop B12 deficiency.

**Table 6: Correlation between type of diet and B12 deficiency.**

B12 deficiency and diet correlation	Diet		Total
	Vegetarian	Non-Vegetarian	
B12 levels	Deficient	4	26
	Normal	70	74
Total	20	80	100

**Difference in MMSE scores**

As per Table 9 the MMSE scores were significantly lower in patients with B12 deficiency 13.42 as compared to those with Alzheimer's 14.3 means and those with multi-infarct state 17.3 means. There was also a significant difference between patients with Alzheimer's disease and multi-infarct state.

As shown in Table 10, MMSE scores measured after 6-8wks of treatment for B12 deficiency. Most patients admitted to our hospital for initiating therapy, and the rest were advised therapy under a physician (mostly local patients), and all asked to review after 6-8 wks. Three patients with B12 deficiency were lost to follow up, and the MMSE could not be measured.

Of those who followed up, the mean improvement in MMSE was from 13.87 to 23.5, which is an improvement by 9 points, which is significant considering the average

MMSEs of other types. The best development was by 12 points in 1 patient, and the least was by 4 points in a patient who had a concomitant multi-infarct state. This improvement in MMSE after treatment was more marked in those with isolated B12 deficiency as compared to those with B12 deficiency associated with other co-

morbidities like multi-infarct disease or Alzheimer's disease ( $p < 0.001$ ). In terms of absolute values, in isolated B12 deficiency, there was an improvement by 9 points versus 5 points for B12 lack associated with other comorbidities.

**Table 9: MMSE score differences.**

MMSE scores	All patients	Alzheimer's	Multi-infarct disease	Isolated B12 deficiency	Mixed B12 deficiency
Mean	15.33	14.3	17.33	13.42	13.80
Standard deviation	2.66	1.6	2.2	1.6	1.35
Minimum		12	14	11	12
Maximum		17	21	16	16

**Table 10: MMSE analysis before and after treatment with B12 injections.**

MMSE domains	B12 deficiency (n=26) Before	B12 deficiency (n=26) after	Mixed
Orientation (10)	5.2	8	6.8
Registration (3)	1.47	2.5	2.1
Calculation (5)	1.8	4.5	3.5
Recall (3)	1.6	2.5	2.2
Language and drawing (9)	3.8	6	4

## DISCUSSION

This study was a prospective study in a Konaseema, Amalapuram, Andhra Pradesh population recruiting 100 elderly patients (>60 years) with dementia and studying the causes for dementia and estimating the prevalence of B12 deficiency as the cause of dementia and also to assess the effects on MMSE after treatment. Most of the patients complained of the inability to walking, muscle weakness, anorexia, and paresthesias. The most frequent finding was peripheral neuropathy due to diabetes and B12 deficiency.

In this study, the population selected was above 60 years, and most of them were between the 60-69 year groups and were predominantly males 70%. All of them had dementia as defined by MMSE less than 21. The average duration of dementia was  $38.01.2 \pm 17.7$  months. There was a significant difference in the duration between the various groups of dementia. Alzheimer's dementia was the most prolonged duration with a mean of 76 months followed by multi-infarct- 46 months and B12 deficiency- 16 months (average  $11.6 \pm 1.4$ ). This finding was in keeping with the studies done by Nagaraja et al, in India, where the duration of dementia was shorter in the B12 deficient group compared to degenerative dementias.<sup>9</sup> The duration in the previous CMC study was 10.3 months. The implication is that reversible causes, including B12 deficiency, needs to be suspected in the setting of recent onset rapidly progressing dementia.

### Cause of dementia

Irreversible dementias were the most frequent cause of accounting totally for about 69 cases, and reversible dementias accounts for 20% of cases. Nearly 11% were due to mixed reasons; that is, they had both a reversible cause (B12 deficiency and combined Total 31%) and irreversible cause (either multi-infarct or Alzheimer's).

Compared to prior studies, there was a marked difference in our results. As compared to the survey by Hejl et al, the most frequent causes of reversible dementia were depression and alcohol-related.<sup>10</sup> In the same study, the reversible causes accounted for 19% cases. In the meta-analysis, 13% had reversible causes, and again the most frequent reasons were drugs, depression, and metabolic causes.<sup>11</sup>

Among the irreversible causes, the commonest was vascular dementia (37.5%) followed by Alzheimer's (20%) which is in keeping with the study done by Rajkumar et al, in the suburbs of Chennai, Varghese et al, in rural Kerala and SGPGI study.<sup>12,13</sup> This finding in the study substantiates the fact that vascular dementia is the most frequent cause of dementia in the Indian population.

### MMSE values

The average MMSE in our study population was 16 and 90% of the patients were between 14-20. Hence most of our patients were severely demented. The average MMSE

values showed significant differences between the groups.

The lowest MMSE recorded for reversible dementia due to B12 deficiency (13.42) whereas the irreversible dementias had better scores (Alzheimer's-14.32 and multi-infract-17.33). This finding was contrary to what was found by Nagaraja et al.<sup>9</sup> This finding probably was because the B12 deficient patients who presented to us were in an advanced stage, as evidenced by the large proportion of the neurological conclusions, including myelopathy, neuropathy, and optic neuropathy. The least MMSE scores, in our study, were in the mixed B12 deficient group, which had associated irreversible causes.

### ***B12 deficient patient profile***

This group accounted for 31% of cases and divided into two different causes isolated B12 deficiency, which was 20% and B12 deficiency associated with irreversible reasons, which was 11%. In other international studies mentioned earlier (14,15), the frequency of B12 deficient dementia varied between 9-25%. In additional Indian education, the rate was 7% and the sample size was around 100. Yajnik's study found a high proportion of patients with asymptomatic B12 deficiency (up to 60% in the rural population).<sup>16</sup> Many patients complained of paraesthesia (19%) and anorexia (19%), which were the main two symptoms in this group. 12 patients also reported psychiatric symptoms. As mentioned, it is interesting to note that many patients had neurological manifestations. All had dementia, and a majority had peripheral neuropathy (35%)-mainly sensory. Many also had features of hemiplegia 31%, myelopathy (18%), and optic atrophy (11%).

### ***Laboratory features of B12 deficiency***

In our study, the B12 assay taken as the gold standard and a value of less than 150 pmol/L considered being very low. MCV, peripheral blood smears were two useful markers for B12 deficiency. They all had low sensitivities but had very high specificities (>95%). Hence, if present in high values, they point towards B12 deficiency. Also, it is essential to remember that a normal MCV, PBS does not rule out B12 deficiency. In our study, of all those with B12 deficiencies, five patients had average or lower values of MCV, 3 cases normal 3 cases dimorphic 2 cases hypochromic in PBS. This study was less to the findings of the CMC study in which 17% had normal MCV.<sup>17</sup>

### ***Changes after B12 administration***

There was follow up available only in 24 out of the 26 B12 deficient patients. There was a significant improvement in MMSE by an average of 7 points overall. When this further split up, there was an improvement by 9 in the isolated B12 deficiency group and by only 5 in the mixed group. This data suggests that in patients with mixed etiology, the irreversible causes contributed more

to dementia than B12 deficiency. The symptoms of anorexia and peripheral neuropathy showed significant improvement in 6-8 wks after treatment, and there was minimal improvement in myelopathy and ataxia as well, but this probably needs longer to follow up. Optic Neuropathy: This symptom did not show any improvement.

In a study from Lebanon, to assess the improvement in cognition after B12 replacement found that after 12 months of treatment, 40 of 56 patients revealed cognitive improvement.<sup>8</sup> There was a prominent correlation between the duration of cognitive symptoms and response to therapy.<sup>18</sup> Patients symptomatic for <12 months gained an average of six points on the MMSE (paired t-test P = 0.0065), whereas patients symptomatic >12 months gained an average of four points (paired t-test p = 0.25). Similar reversibility observed in other studies from UK.<sup>8</sup> There are also other reports to suggest that supplementing B12 causes improvement in the blood-brain barrier and thus stabilizing cognitive functions.

## **CONCLUSION**

In our study population, vascular dementia (44%) was more common than Alzheimer's (17%). The distribution of reversible dementias was much higher (31%) than other earlier

Studies and the most common among these was Isolated B12 deficiency (20%). The average duration of the presentation was much shorter in B12 deficiency (10-12 months, mean 11.6±1.4). MMSE was lower in B12 deficiency compared to irreversible causes. Thus, severe dementia, shorter duration, focal neurological signs, and a vegetarian diet are significantly associated with the development of B12 deficiency. B12 deficiency seems to affect registration and calculation, whereas Alzheimer's seems to change orientation and recall. There was a significant improvement in MMSE after treatment in pure B12 deficient patients (by 9 points) if they presented within one year of symptoms. There was an improvement in other neurological parameters except for myelopathy. Hence Considering this improvement and a high prevalence of B12 deficiency in the elderly Population, we suggested that B12 levels be done for all elderly dementia patients as it is a treatable cause, which can make a marked improvement in a patient's memory and quality of life.

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