

A study on estimating the prevalence of vitamin B12 deficiency in elderly population with dementia

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Abstract

Aim & Objective: The aim of our study was to determine the prevalence of major types of dementia in our population and to specifically look at the prevalence of B12 deficient dementias. **Methodology:** A prospective cohort study involving 100 elderly patients with dementia. **Results:** In our study population, vascular dementia (38%) was more common than Alzheimers (20%) probably due to the high prevalence of diabetes and hypertension. The proportion of reversible dementias were much higher (25%) than other earlier studies and the most common among these was B12 deficiency (19%). The average duration to presentation was much shorter in B12 deficiency (10 months). MMSE was much lower in B12 deficiency (13) compared to irreversible causes (16). Thus shorter duration, severe dementia, focal neurological signs and vegetarian diet was significantly associated with development of B12 deficiency. In the diagnosis of B12 deficiency, MCV, peripheral blood smear and LDH had relatively low sensitivities (62.5%, 71% & 72.4% respectively) but very high specificities (98.7%, 96.9% & 97.5% respectively). B12 deficiency seems to affect more of registration and calculation whereas Alzheimer's seems to affect more of orientation and recall. There was a significant and marked improvement in MMSE after treatment in pure B12 deficient patients (by 10 points) if they presented within 1 year of symptoms. There was improvement in other neurological parameters except myelopathy. Multi-infarct state was significantly associated with risk factors- diabetes, hypertension, dyslipidemia, non-vegetarian diet and alcohol intake. **Conclusion:** Considering this marked improvement and a high prevalence of B12 deficiency in elderly population, we recommend that B12 levels to be done for all elderly dementia patients as it is a potentially treatable cause which can make marked improvement in a patient's memory and quality of life.

Keywords: Vitamin B12, Dementia, MMSE, Prevalence, Hypertension, Diabetes.

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Introduction

Dementia is defined as an acquired impairment of memory and intellectual functioning, which is not associated with fluctuations in the level of consciousness.[1] It must be differentiated with delirium which has a different set of causes. Dementia is a common problem in the elderly with the prevalence increasing with age and approaching 40% in patients above 80 years of age. It is a major cause of morbidity in the elderly. With the increasing life expectancy in India (currently 65 years), we can expect to encounter more and more cases of dementia. The vast majority of cases of dementia are degenerative or vascular in nature and are usually relentlessly progressive with few therapeutic measures for treatment available. Hence the importance of detecting the reversible causes of dementia. There are only a few reversible causes of elderly dementia of which vitamin B12 deficiency is the most easily treatable one. It is well known that B12 deficiency can cause isolated dementia and that it can be a coexisting factor in other irreversible dementias. Hence this study focuses on studying the prevalence of various types of dementia in the elderly population presenting to a tertiary care of

hospital in South India and specifically looking at the prevalence B12 deficiency and studying the profile of B12 deficient patients. We also aim to look at the risk factor profile of patients with vascular dementia, which is the most common cause of dementia[2-4].

Aim of the study: The aim of our study was to determine the prevalence of major types of dementia in our population and to specifically look at the prevalence of B12 deficient dementias.

Patients and methodology

Study setting: The study was conducted in Shadan Medical College & Hospital, Hyderabad, Telangana. Eligible subjects were recruited from the departments of Medicine and Neurology. Currently, the department of Medicine has daily out patient days (OPD) and Neurology has thrice week OPD .

Study design: A prospective cohort study involving 100 elderly patients with dementia .The study design and methods were approved by the Research Committee (Institutional Review Board) of Shadan Medical College, Hyderabad.

Subjects: Subjects were elderly patients above 60 years of age who were recruited from the 2 departments as mentioned earlier. The patients were residents of Telangana.

Inclusion criteria

Elderly patients more than 60 years of age, who were literate and had Dementia as per DSM-V criteria and MMSE <24.

Exclusion criteria

- Delirium presentation
- Recent vitamin B12 injections or chronic vitamin users

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- Recent history of blood transfusions
- Acute alcohol intoxication/ withdrawal
- Chronic bed bound, malnourished multi-infarct dementias

Subject enrollment: Ours was a prospective cohort study done between January 2016 to June 2017. All patients who presented to OPD with complaints of dementia (satisfying the inclusion criteria) were included in the study and evaluated further with detailed history, examination and MMSE. (as shown in proforma).

Methodology: The patients were asked in detail about the duration of dementia, presence of paraesthesia, anorexia, skin darkening, ataxia and visual and psychiatric problems in the past. The risk factor profile in terms of diabetes, hypertension, IHD, dyslipidemia, diet (vegetarianism) and the mean duration in months were recorded. Any significant drug history and duration of smoking in pack years were also recorded. The patients also underwent a detailed general and neurological examination. The specific type of dementia was diagnosed based on clinical criteria and laboratory data. Subsequently, the patients were given investigations which included complete hemogram, peripheral blood smear, MCV, TSH, HIV ELISA, VDRL, B12 and folate levels, LDH, B12 levels and neuroimaging when indicated. By definition, severe B12 deficiency was diagnosed when the B12 levels were less than 150pmol/L based on our lab's colorimetric assay. A level of 150-200 would indicate mild deficiency and above 200 was considered normal. In our

analysis, we have included only severe B12 deficiency (<150pmol/L).

After a diagnosis of B12 deficiency was made, the patients were either offered admission here or in a local hospital of the patient's convenience for treatment with B12 injection. The standard B12 schedule was followed, starting with daily intramuscular injection of B12 1000mcg for a week followed by once a week for 1 month and then to continue once a month. The patients were asked to come back for follow up after 6-8 wks of treatment for a repeat MMSE[5-7]

Statistical analysis: Data entry was done using the Statistical Package for the Social Sciences (SPSS) software package (version 15). Descriptive statistics were calculated using SPSS software. Chi-square test was used for comparison of categorical variables. Odds ratio (OR) and confidence intervals (CI) were calculated and a p value less than 0.05 was considered statistically significant.

Results

Demographic data: During the study period, a total of 100 patients were recruited into the study. Of these, 68(68%) were males. The age and sex distribution of the study population is shown in Table 1, and represented in Figure F. All patients were more than 60 years of age, with maximum being in the 60-70 year age category (70%). Only 5 percent were older than 80 years. The differences between the age groups were not significant (P- 0.67), since most of our patients were in 60-69 age group across all causes of dementia. Thus no increasing trend was noticeable between the various groups

Table 1: Age distribution of the study population: p =0.670

Age	Frequency(Percent)	ALZHEIMER'S	MULTI INFARCT	B12 DEF	MIXED
60-69	71(71.0%)	15	26	7	5
70-79	24(24%)	4	11	3	2
>80	5(5%)	1	1	1	1
Total	100(100%)	20	38	11	8

Table 2 : Department wise distribution

Department	No. of Patients
Neurology	70
General Medicine	30

Table 3 : Duration of dementia

Duration of dementia(in months)	All patients	Alzheimer's	Multi infarct disease	Isolated B12 deficiency	Mixed B12 deficiency
Median	36	54	42	10	60
Mode	36	36	36	8	60
Mean(±) S.D.	41.2±17.6	53.60±18.06	40.87±9.93	10±4.93	58.94±15.33
Minimum	12	24	24	3	36
Maximum	90	90	66	18	84
Percentiles					
	25	30	36	6	48
	50	36	54	10	60
	75	48	70.5	14	72

Patient clinical profile

Dementia duration: The average duration of dementia across all categories was 41.2 months. By individualizing the dementia duration with the final diagnosis, it was found that the average

duration for Alzheimer's was the longest (53.60 months) followed by multi infarct state (40.87 months) followed by B12 deficiency (10 months). The difference in means among the all 4 groups was statistically significant (p=<0.001 by ANOVA)[8-10]

Table 7: Frequency of clinical features (symptoms)

Complaint	Total	ALZHEIMER'S	Multi Infarct	B12 DEF	MIXED	p
Paraesthesia	17%	1	2	9	5	<0.001
Anorexia	18.5%	1	1	10	6	<0.001
Hyperpigmentation	7.5%	0	1	4	2	<0.001
Muscle weakness	35.5%	2	27	1	5	<0.001
Imbalance	53%	5	30	9	9	<0.001
Vision problems	11%	2	2	5	1	<0.001
Psychiatric symptoms	12%	4	2	2	3	0.120
Diarrhea	3%	0	0	2	1	<0.001

Symptoms other than dementia

The commonest next symptom was imbalance which was seen in more than half the number of patients followed by muscle weakness which was mostly due to prior infarct, presenting as hemiparesis or hemiplegia. An equal number reported paraesthesias and anorexia. Very few had reported psychiatric symptom or visual problems.As

seen from table 7, the symptoms of paraesthesia, anorexia, hyperpigmentation, vision problems and diarrhea were significantly more common in B12 deficiency group whereas difficulty in walking and muscle weakness was significantly common more in the vascular dementia group.

Table 8 : Comorbidity profile

Comorbidity	Frequency N	(%)	Mean Duration in months	Alzheimer's	Vascular	B12 DEF	MIXED	P value
DM	47	(47)	67.59	4	26	3	6	<0.001
HTN	52	(52)	56.35	6	31	5	5	<0.001
IHD	7	(7)	40.29	1	5	0	1	0.10
Dyslipidemia	29	(29)	45.79	2	21	3	2	<0.001
CVA	32	(32)	33.47	0	26	0	4	<0.001

Comorbidities:The comorbidity profile among the 200 patients are shown in table 8 and figure I.This shows that majority of the elderly population in this study were diabetic or hypertensive, and hypertensives were slightly more than the diabetics. The average

duration in months were 67 and 56 months respectively. The risk factors (except IHD) were significantly associated with vascular dementia. Only 32% had reported a previous event of stroke.

Table 4: Frequency of clinical features (signs)

Sign	Frequency (%)	alzheimers	vascular	B12 def	mixed	P value
Pallor	11 (11)	1	4	4	2	0.003
Glossitis	8 (8)	0	1	6	2	<0.001
Pedal Edema	2 (2)	0	0	2	0	0.099
Optic neuropathy	5 (5)	0	1	5	0	<0.001
Peripheral neuropathy	17 (17)	1	0	10	6	<0.001
Myelopathy	8 (8)	0	0	6	2	<0.001
Ataxia	18 (18)	1	1	13	3	<0.001
Gait not assessed	10 (10)	10	31	10	7	<0.001
Hemiplegia	42 (42)	0	35	0	8	<0.001
Cerebellar signs	2 (2)	0	1	2	0	0.055
Bilateral stroke signs	10 (10)	0	8	0	2	<0.001

Clinical features

The clinical features (signs on examination) are shown in table 4 and represented in figure J.The most common finding during examination was hemiplegia. Peripheral neuropathy and myelopathy accounted for many cases as well. Many cases of multi- infarcts had bilateral

pyramidal signs and the gait could not be assessed in these patients.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.

Table 5: Clinical profile of all B12 deficient patients

Sign/symptom	N (%)
Hyperpigmentation	6(31.6)
Paraesthesia	13(65.8)
Diarrhea	2(13.2)
Anorexia	14 (76.3)
Psychiatric symptoms	3(13.2)
History of gastrointestinal surgery	2(10.5)
Pallor	5 (28.9)
Glossitis	7(36.8)
Optic neuropathy	4(21.1)
Myelopathy	8 (42)
Peripheral Neuropathy	10 (50)

Clinical profile of B12 deficient patients:The clinical features of B12 deficient patients are shown in table 6 and represented in figure L.History of paraesthesia and anorexia were the most frequent symptom in all B12 deficient dementia patients. The next commonest symptom was skin hyperpigmentation and few patients also had psychiatric manifestations.2 patients gave prior history of GI surgery which probably was the cause of B12 deficiency in these patients (small bowel surgeries, thus affecting B12 absorption) On examination, 5 had pallor and 7 had glossitis. 4 patients had optic neuropathy due to B12 deficiency of which 3 were documented by

the ophthalmologists.Neurological involvement was quite common in our study. 4 patients satisfied the criteria for subacute combined degeneration. 10 (50%) patients had features of peripheral neuropathy which was predominantly more sensory. 8 (42%) patients had myelopathy. Totally 11 (68%) patients had other neurological findings other than the syndrome of dementia. Neuropsychiatric symptoms were seen in 2 patients which included depression, hypomania, paranoid psychosis with auditory or visual hallucinations.

Table 6: Correlation between peripheral blood picture and B12 deficiency: (p<0.001)

	Peripheral blood smear				Total
	Normal	Hypochromic Microcytic	Megaloblastic	Dimorphic	

B12 normal	72	8	1	0	81
deficient	4	1	13	1	19
Total	76	9	14	1	100

As seen in table 6, 13 out of 19 patients had a megaloblastic blood picture, with, hypersegmented neutrophils, basophilic stippling, ovalocytes and macroovalocytes. The association between B12 deficiency and megaloblastic blood picture was significant

(p<0.001). 4 patients had a normal blood picture though their B12 levels were very low. And 1 patient had a dimorphic blood picture with both megaloblastic and microcytic changes. Only 1 patient had hypochromic and microcytic blood picture despite low B12 levels.

Table 7: Anemia in the study population: (P=0.011)

		Normal	B12 deficient	Total
Hb	Anemia	20	8	28
	Normal	61	11	72
Total		81	19	100

Out of the 100 recruited, 28 had anemia. As seen in table 8, there was a significant correlation of anemia with B12 deficiency, in that, there

was a higher proportion of anaemic patients in the B12 deficient group.

Table 8: CT/MRI findings in B12 deficient patient

	Frequency	Percent
Normal	8	43.0
Cerebral atrophy	2	14.0
Multiple Infarcts(small vessel disease)	6	30.0
Volume loss and hippocampal atrophy	2	8.0
Miscellaneous	1	5.0
	19	100

For patients with isolated B12 deficiency patients, neuroimaging was normal. 28.9% and 7.9% had features of multi-infarct and alzheimer's respectively on neuroimaging. The features on MRI/CT to suggest a multi-infarct state was either multiple small lacunar infarcts or

periventricular hyper intensities suggestive of small vessel disease. The neuroimaging features of Alzheimer's were either a normal imaging or features to suggest volume loss and hippocampal atrophy.

Table 9: MMSE score differences

	Frequency	Percent
Normal	8	43.0
Cerebral atrophy	2	14.0
Multiple Infarcts(small vessel disease)	6	30.0
Volume loss and hippocampal atrophy	2	8.0
Miscellaneous	1	5.0
	19	100

Table 10: MMSE scores before and after (6wks) of B12 correction

P =<0.001	MMSE before Rx	MMSE after Rx
N Valid	19	19
Mean	13.34	21.10
Median	14.00	20.00
Mode	15	18(a)
Std. Deviation	1.935	4.670
Minimum	10	14
Maximum	16	29

The mean improvement in MMSE was from 13.34 to 21.10, that is a improvement by 8 points which is a significant considering the average MMSEs of other types. The best improvement was by 13 points in 1 patient and the least was by 4 points in a patient who had concomitant multi-infarct state.

Discussion

This study was a prospective study in an Indian 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. In this study, the population selected was above 60 years and most of them were between the 60-70 year group and were predominantly males (68.5%). All of them had dementia as defined by DSM V and MMSE less than 24. The average duration of

dementia was 41 +/- 17 months. There was a significant difference in the duration between the various groups of dementia. Alzheimer's dementia was the longest duration with mean of 53 months followed by multi-infarct- 40 months and B12 deficiency- 10 months. This finding was in keeping with the study done by Nagaraja et al in India. Vascular dementia patients are mostly associated with diabetes and hypertension and dyslipidemia and had history of cerebrovascular accidents. In community-based studies in Europe, the incidence of VaD has ranged from 0.17 to 0.71 per 100 person-years[3].

Cause of dementia

In our study, irreversible dementias were the commonest cause accounting totally for about 68% of cases and reversible dementias accounts for 25% of cases. Nearly 7% were due to mixed causes i.e., they had both a reversible cause (B12 deficiency) and irreversible cause (either multi-infarct or Alzheimer's). In the largest and earliest

single study by Hejl et al [4], 1000 pts referred to a university hospital were prospectively evaluated to assess the prevalence of dementia based on etiology. The mean age at enrollment was 66 yrs (range 17 to 98), and 43% met the diagnostic criteria for dementia. 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. Least MMSE score recorded for B12 deficiency is 10 and the maximum score recorded is 16. Least MMSE score recorded for alzheimer's is 13 and the maximum score recorded is 19. The test is not sensitive for mild dementia, and scores may be influenced by age and education, as well as language, motor, and visual impairments [5]. The use of higher cutoff scores on the MMSE improves sensitivity but lowers specificity. For research purposes, some investigators use a cut off score of 26 or 27 in symptomatic populations in order to miss few true cases, while lower cut offs could be necessary in populations where the expected prevalence is low [6]. Some groups have developed tools that incorporate age, gender, and education level as shown below [7,8]: Least MMSE score recorded of multi infarct dementia was 14 and the maximum score recorded was 19, the average MMSE score was 16 and had a bell shaped distribution. The average MMSE values showed significant differences between the groups. The lowest MMSE was recorded for reversible dementia due to B12 deficiency (13.62) whereas the irreversible dementias had better scores (alzheimer's-15.95 and multi-infarct state-16.98). There was also significant difference between the patients with alzheimer's disease and multi infarct state ($p=0.01$). This finding was contrary to what was found by Jha et al [9]. This probably was due to the fact that the B12 deficient patients who presented to us were in an advanced stage of the disease as evidenced by large proportion of neurological findings including myelopathy, neuropathy and optic neuropathy. There is no significant difference in orientation, recall, language and drawing between alzheimer's and B12 deficiency. There is no significant difference in registration, calculation, recall, language and drawing in between alzheimer's and multi infarct dementia, there is no significant difference in language and writing between vascular dementia and B12 deficient patients. Registration, recall and calculation are preferentially affected in multi infarct dementia. B12 deficiency, in our study, seems to affect preferentially more registration and calculation and Alzheimer's affects more of orientation and recall. The clinical significance of this may not be relevant as the differences are in decimal points only since each domain can have maximum of 3-5 points only. Hence this may be just a trend seen in our study and would need further validation using a larger sample size. Majority of the elderly population in this study are diabetics and hypertensives. Hypertensives are slightly more than diabetics. B12 deficient dementia patients do not show much association with comorbidities like diabetes and hypertension. These risk factors (DM/HTN/dyslipidemia/CVA) are significantly associated with vascular dementia. The features of glossitis, optic neuritis, neuropathy, ataxia, myelopathy are significantly more in B12 deficient group whereas stroke signs were much more common in the vascular dementia group. Most common finding in these patients during examination in all dementia patients was hemiplegia. Peripheral neuropathy and myelopathy accounted for many cases as well. Many cases of multi infarcts had bilateral pyramidal signs. In B12 deficient patients neuropsychiatric symptoms were seen in 2 patients which includes depression, hypomania, paranoid psychosis with auditory/visual hallucinations.

Changes after B12 administration

There was significant improvement in MMSE by an average of 8 points overall and

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when this was further split up, there was an improvement by 10 in the isolated B12 deficiency group and by only 4 in the mixed group. This suggests that in the patients with mixed etiology, the irreversible causes contributed more to the 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 a longer follow up. This result is in keeping with previous studies in which the neurological symptoms have improved rapidly since the patients presented within 1 year of illness and presence of myelopathy probably indicated a worse prognosis since there was hardly any improvement. But these patients need longer follow up to re-assess myelopathy. These findings correlate with other Indian study by Rachana Agarwal et al [10]

Conclusion

Considering this marked improvement and a high prevalence of B12 deficiency in elderly population, we recommend that B12 levels to be done for all elderly dementia patients as it is a potentially treatable cause which can make marked improvement in a patient's memory and quality of life.

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