Neurological Manifestations of $B_{12}$ Deficiency with Emphasis on its Aetiology

Pradeep G Divate¹, Rashida Patanwala²

Abstract

**Background**: It is believed that Pernicious anaemia (PA) is more common in the West. We postulate however that in India PA is probably an important aetiological factor as a cause of Vitamin $B_{12}$ deficiency in patients having neurological disease.

**Objective**: To investigate the aetiological factors resulting in Vitamin $B_{12}$ (Vit $B_{12}$) deficiency in patients with subacute combined degeneration (SACD) and other neurological manifestations.

**Methods**: We undertook a prospective study of 50 patients, all clinically suspected to have Vit $B_{12}$ deficiency; they were investigated clinically, haematologically, biochemically and radiologically.

**Results**: There was a dominance of males (41 of 50) with the majority in the age group of more than 40 years of age. There was no correlation between the socio-economic and dietary status on the one hand and the clinical manifestation on the other. Anti intrinsic factor antibodies (AIFAB) were positive in 19 of 50 patients (38%) and anti parietal cell antibodies (APCAB) were positive in 28 of 50 (56%) patients.

**Conclusion**: We conclude that Pernicious anaemia is an important cause of various neurological manifestations including SACD in the Vitamin $B_{12}$ deficient population in the age group of more than 40 years, irrespective of the socio-economic and dietary status in the Indian subcontinent. It is supported by the presence of AIFAB or APCAB in this group.

Introduction

All naturally occurring forms of Vitamin $B_{12}$ (Vit $B_{12}$) arise in micro-organisms. Some dietary sources of Vit $B_{12}$ are dairy products, eggs, the liver and kidneys of animals. The daily requirement (RDA) of Vit $B_{12}$ is 2.2 mcg whereas according to the national institute of nutrition Hyderabad, it is 1 micrograms/day in Indians.¹ In general, Indians are vegetarians and hence have low $B_{12}$ levels.

Deficiency of Vit $B_{12}$ occurs because of poor intake and/or malabsorption of dietary cobalamin. The result is demyelination of spinal cord, white matter of the brain and peripheral neuropathy that is preponderantly sensory.

We herein decided to investigate the neurological manifestations of Vit $B_{12}$ deficiency and its aetiology.

Patients and Methods

The patients were recruited from the Indoor and Outdoor Departments of different hospitals. The total number of patients studied was 50 of which 9 were females.

The selected patients met the following criteria –

2. Symptoms suggestive of neurological involvement – paraesthesias and numbness in limbs, difficulty in activities of daily living like writing, buttoning,
mixing food, cutting of bread; loss of balance; difficulty in walking; decreased pace of walking; feeling of walking on cotton/sponge; slipping of footwear; Lhermitte’s symptom; bladder/bowel disturbances; impotence; increased forgetfulness; irritability, frank dementia and mood and behavioural changes.

A detailed history of each patient was elicited with reference to economic status, income category, professional status and diet.

The patients were examined for the following- pallor, icterus, glossy tongue, hyper-pigmentation of knuckles and vitiligo. Detailed neurological examination was carried out of each patient with special attention to sensory examination and gait analysis. The cognitive functions were assessed by mini mental state examination (MMSE).

Once the patients were selected, various haematological parameters including peripheral smear analysis for megaloblasts, macrocytes, hypersegmented neutrophils and RBC indices were carried out. The work up consisted of routine blood biochemistry, protein electrophoresis, lactate dehydrogenase [LDH] (N < 200 I.U.), thyroid function tests, serology for syphilis and HIV. Serum Vit B_{12} and folic acid were estimated by Chemiluminiscence Immunoassay. Vit B_{12} deficiency was said to be present when Vit B_{12} and folic acid were below <200 pg/ml and <3.00 ng/ml respectively.\textsuperscript{2,3}

The patients were subjected to nerve conduction velocities (NCV) by standard techniques. Magnetic resonance imaging (MRI) of spinal cord was done by conventional sequences to rule out compressive or other intrinsic diseases and to look for hyper-intensity of posterior and lateral columns in T2 sequences. Pernicious anaemia was said to be present when antiparietal cell antibodies [APCAB > 10 Units; sensitivity 80%; specificity 50 - 100%] and/or Anti-intrinsic factor antibodies [AIFAB > 1.1 units; sensitivity 50%; specificity 100%] were raised.\textsuperscript{4} Schilling test, as is unavailable in our set up and nearby centers, was not carried out.

In patients with Vit B_{12} values between 200 and 300 pg per milliliter and in the presence of normal folic acid levels, in lieu of estimation of Homocysteine and Methylmalonic acid, ancillary evidences like hypoproliferative anaemia characterised by marked macrocytosis, hypersegmentation of neutrophils, pancytopenia, and signs of ineffective erythropoiesis (such as elevated levels LDH and indirect bilirubin) were assessed.

The standard of living index [SLI] was calculated as per the national family health survey-2 as follows:\textsuperscript{5}


Exclusion criteria in this study were history of diabetes mellitus, alcohol abuse, pancreatitis, gastric or ileal surgery/disease, drug intake like metformin, gastric acid suppressants or exposure to Nitric Oxide and malabsorption syndrome and other causes of spinal cord or peripheral nerve disease; other cause of spinal cord or peripheral nerve disease. Patients with lower motor neuron signs like fasciculations and wasting in the upper limbs were excluded from the study. In the process of selection the following patients were excluded – Cervical myelopathy (7 patients), ataxic neuropathy due to CIDP with M band (1 patient), Chronic inflammatory demyelinating polyneuropathy (2 patients), GBS with ataxic neuropathy (2 patients), Tabes dorsalis (1 patient), Pott’s disease of thoracic and cervical spine (1 patient each).

The selected patients met the following criteria: low serum B_{12} levels, laboratory support of megaloblastic anaemia, clinical signs of recent cognitive decline and myelopathy-neuropathy.

**Results**

The 50 patients predominantly belonged to the middle and elderly age groups (Table 1).

There were 41 males [82\%] and nine females [18\%] (Pie Chart 1).

In the study group, 21 were vegetarians [42\%], 12 were ovolactovegetarians [24\%] and 17 were nonvegetarians [34\%] (Pie Chart 2).

Forty patients belonged to the high SLI category [80\%] and ten belonged to medium SLI [20\%].

Of the 50 patients, the commonest symptom

<table>
<thead>
<tr>
<th>Physical finding</th>
<th>No of Patients</th>
<th>%</th>
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<tbody>
<tr>
<td>Knuckle pigmentation</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>Pallor</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>Icterus</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>2</td>
<td>4</td>
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<th>Table 2 : Symptoms observed in the studied Patients</th>
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<tr>
<td>Symptom</td>
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<tr>
<td>No of Patients</td>
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<tr>
<td>%</td>
</tr>
<tr>
<td>Paraesthesias</td>
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<tr>
<td>Loss of balance</td>
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<tr>
<td>Difficulty in walking</td>
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<tr>
<td>Mental changes</td>
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<td>Lhermitte’s symptom</td>
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<td>Impotence</td>
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<th>Table 3 : Physical findings observed in the patients</th>
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Forty patients belonged to the high SLI category [80\%] and ten belonged to medium SLI [20\%].

Of the 50 patients, the commonest symptom
was paraesthesias, followed by loss of balance and difficulty in walking (Table 2).

Stomatitis was observed in 29 patients (58%).

The majority had symptoms of less than six months and most below one year of duration.

The most common physical finding was knuckle pigmentation followed by pallor and icterus (Table 3).

The Neurological disability was calculated as per the disability scoring which is as follows*

**Gait Disturbances**

GR. 0 – Normal gait. GR. 1 – Unable to maintain Romberg position. GR. 2 – Impairment but able to walk unsupported. GR. 3 – Support required for walking. GR. 4 – Wheelchair or bedbound.

**Sensory Disturbance**

GR. 0 – No sensory disturbances. GR. 1 – only in toes and fingers. GR. 2 – in ankle and wrists. GR. 3 – in upper arms and legs.

**Mental Disturbances**

GR. 0 – Normal mentation. GR. 1 – intellectual impairment but needs no social support. GR. 2 – Partially dependent for activities of daily living. GR. 3 – Completely dependent for Activities of Daily Living [ADL].

**Neuropathy**

GR. 0 – Absence of neuropathy. GR. 1 – Loss or reduction of ankle jerk. GR. 2 – Loss or reduction of patellar jerk. GR. 3 – Loss or reduction of reflexes in the arms.

**Pyramidal Tract Dysfunction**

GR. 0 – Absence of pyramidal tract damage. GR. 1 – Positive Babinski’s sign. GR. 2 – Spastic paraparesis. GR. 3 – Spastic Tetraraparesis (Table 4).

Haemoglobin values were assessed in 50 patients (Table 5). It was observed that three patients had thrombocytopenia.

High Mean Corpuscular Volume (MCV) was found in 36 patients [72%]. The highest MCV was 121.6. On peripheral smear macrocytes were seen in 30 patients [60%]. Raised LDH values were observed in 34 patients [68%]. Of the two, MCV is probably slightly more often abnormal than LDH (Table 6).

All the patients had normal values of blood sugar, blood urea, serum creatinine, protein electrophoresis and liver function tests.

Low Vit B\textsubscript{12} values were noted in 41 patients [82%] and low Vit B\textsubscript{12} with low folic acid in 7 [14%]. There were nine patients in our series who had Vit B\textsubscript{12} above 200pg /ml - six were between 200 and 300 pg/ml and in two, the values were above 300 pg/ml. Of these nine, macrocytosis with hypersegmented neutrophils were seen in six patients and raised LDH.
Table 8: Anti-Intrinsic Factor Blocking Antibodies (AIFAB) and Anti-Parietal Cell Antibodies (APCAB) as observed in 50 patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No. Of Patients</th>
<th>Age Groups (in years)</th>
<th>Dietary Habits</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIFAB Positive</td>
<td>4</td>
<td>20-40</td>
<td>Veg</td>
</tr>
<tr>
<td>Both AIFAB and APCAB Positive</td>
<td>15</td>
<td>40-60</td>
<td>Veg</td>
</tr>
<tr>
<td>APCAB Positive</td>
<td>13</td>
<td>&gt; 60</td>
<td>Vegans</td>
</tr>
<tr>
<td>AIFAB and APCAB Negative</td>
<td>18</td>
<td></td>
<td>Non-Veg</td>
</tr>
<tr>
<td>TOTAL</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

We studied the Anti-intrinsic factor antibodies (AIFAB) and Anti-parietal cell antibodies in 50 patients (Table 8).

Of the 50 patients AIFAB and APCAB were both elevated in 15 (30%) and AIFAB alone was elevated in 4 (8%) and APCAB alone was elevated in 13 patients (26%). Of the remaining 18 patients, 13 were vegetarians, 2 were non vegetarians and 3 were ovolactovegetarians.

Nerve conduction studies were carried out in 43 patients. Twenty-six patients (56%) had evidence of sensory-motor neuropathy (SMN), three (6.5%) had changes suggestive of predominantly motor neuropathy, six had evidence suggestive of pure sensory neuropathy and only one patient had evidence of radiculopathy. Ten patients (23%) showed changes of axonal degeneration and thirteen (30%) showed changes of demyelination. The nerve conduction studies were normal in seven patients. Although pure motor neuropathy is not a feature of B12 deficiency, the occurrence of motor neuropathy observed in the three patients is intriguing and inexplicable (Table 9).

MRI spine was done in 41/50 patients. Of these 26 patients (63%) had hyper-intensities in the posterior columns in T2 sequences, mainly in the cervical region. Follow up MRI of patient no. 2 showed disappearance of hyperintensities after ten months and that of patient no. 7 showed decrease of the hyperintensities in T2 sequences after eleven months.

After establishing the diagnosis, all the patients were treated with injectable Vit B12, 1000 micrograms/day intramuscularly for ten days, and were maintained on monthly injection of the same dose for few months and later on once in three to six months; oral B complex preparations were simultaneously administered.

Thirty nine patients were followed at varying intervals ranging from two months to one year; eleven patients were lost to follow up. Most patients showed attenuation of paraesthesias but they persisted with decreasing intensity. Stomatitis disappeared completely in all the patients. Imbalance of gait improved remarkably and early; signs of neuropathy and pyramidal signs gradually disappeared over few months. By the end of one year; most patients, barring sensory symptoms were free of their disabilities (Table 10).

An elderly lady presented with dementia. After treatment, there was significant improvement in her memory to allow independent activities of daily living.

Discussion

Pernicious anaemia is the end stage of an autoimmune disorder in which parietal cell antibodies against H+-K+-adenosine triphosphatase cause loss of gastric parietal cells. The loss of parietal cells initially reduces and then completely prevents production of intrinsic factor. In addition, blocking autoantibodies can bind to the B12 binding site for intrinsic factor and prevent the formation of the Vit B12-intrinsic factor complex. Deficiency of intrinsic factor gradually results in Vit B12 deficiency.

Vitamin B12 is a required coenzyme for two important enzymatic reactions. In the first reaction, cobalamin facilitates the methylation of homocysteine by methyltetrahydrofolate into methionine and tetrahydrofolate. Tetrahydrofolate is necessary...
The metabolites of Vit B\textsubscript{12} deficiency, homocysteine and methylmalonic acid, were not tested in the present study as the patients selected had definite manifestations of B\textsubscript{12} deficiency, both clinically and by other investigatory parameters. Of note, all the patients showed unequivocal improvement by the treatment administered; a therapeutic trial and follow up with clinical improvement of signs and symptoms obviates the need of studying these metabolites in Vit B\textsubscript{12} deficiency.\textsuperscript{5} The study of metabolites is indicated when the Vit B\textsubscript{12} values are in the lower limits of normal (200 to 300 pg/ml) and when subtle deficiency is a likelihood.\textsuperscript{7-8}

Besides studying homocysteine would have escalated the cost while providing no additional benefits.

In this study, anti-parietal antibodies (APCAB) were elevated in 28 of 50 patients (56%) and anti-intrinsic factor antibodies (AIFAB) were elevated in 19 of 50 patients (38%).

A similar study carried out earlier showed pernicious anaemia as the cause of sub acute combined degeneration in Indians.\textsuperscript{9}

Pernicious anaemia is the most common cause of Vit B\textsubscript{12} deficiency in the West. In the West, the APCAB are elevated in 90% of patients and AIFAB are positive in 50% of patients.\textsuperscript{10} It was initially thought that pernicious anaemia was restricted to the Northern European population. However, subsequent studies have reported the disease in black and Latin-American subjects, with an earlier age of onset in black women.\textsuperscript{11}

Pernicious anaemia has also been reported among Indians, though rarely; most of the publications describe isolated cases of them.\textsuperscript{12, 13}

Some Indian workers have also compiled data on Vit B\textsubscript{12} deficiency and neurological disease.\textsuperscript{14, 15} The Vellore group studied 63 cases of Vit B\textsubscript{12} deficiency. Anti-intrinsic factor antibody was positive in 19 (76%) and anti-parietal cell antibody was positive in 17 (68%) out of the 25 patients in whom the test was carried out.\textsuperscript{12}

Most of the patients in our study presented with paraesthesias, loss of balance and stomatitis over a duration of three to six months. Some of them had difficulty in walking and one of them presented with frank dementia. Once the diagnosis was established, they were put on Vit B\textsubscript{12} supplements; most showed significant improvement in their presenting symptoms. Complete disappearance of stomatitis was seen in one after month of treatment. Dementia in one patient improved by nearly 90% after five months of treatment.

We observed male predominance (82%) in our study of 50 patients. This male predominance is puzzling; similar observation has also being made by others.\textsuperscript{12}

In our study, 21 were vegetarians, 12 were ovolactovegetarians and 17 were non vegetarians. In most of the previous studies, the majority were vegetarians. All the patients of Jeejebhoy et al\textsuperscript{14} and Wadia et al\textsuperscript{15} showed that vegetarians predominated the study population. In Wadia and Swami’s series, 9 out of 14 patients were vegetarians.\textsuperscript{16}

As alluded to, in the West the APCAB are elevated in 90% of patients and AIFAB are positive in 50% of patients.

The cause of Vit B\textsubscript{12} deficiency and neurological manifestations in our cases appear to be due to age, pernicious anaemia, dietary habits and hitherto unknown factors.

In the present study, 20 (40%) were from age group 41-60 years, 18(36%) were from age group > 60 years and 12 (24%) were in the age group, 15-40 years. As age advances, the cobalamin levels get lowered.

Lindenbaum reported a 12% prevalence of cobalamin deficiency among elderly participants in the Framingham study.\textsuperscript{17} The low cobalamin levels in the elderly are attributed to loss of acidity resulting from type B atrophic gastritis; the last may affect 40% of the elderly and is associated with impaired absorption of protein bound Vitamin B\textsubscript{12}.\textsuperscript{18}

The cobalamin levels are low in vegetarians, besides malnutrition is common in India; however most persons are asymptomatic. Indeed, the expatriate as well as Indians at home show cobalamin deficiency.\textsuperscript{19, 20}

We observed that dietary differences did not influence the clinical presentation. There were 21 vegetarians, 12 ovolacto vegetarian and 17 non-vegetarians. Majority of these patients belonged to middle- higher middle class of society as per standard living index. Therefore, it appears as though dietary deficiency may not be the sole factor in causing cobalamin deficiency in the middle income group that we studied.
We would like to postulate pernicious anaemia as a cause of SACD on the basis of the following points:

1. Age of onset > 40 years in the majority; pernicious anaemia usually does not appear before the age of 30 in adults. The average age at diagnosis is around 60 years.
2. Absence of correlation between the socio-economic and dietary status to the clinical manifestations.
3. In a wide population of Vitamin B₁₂ deficient patients, only a small section manifests as SACD; among others pernicious anaemia seems to be one such causative factor.

This is an essentially small observational study; in a large country like India the population is heterogeneous, having diverse dietary habits and hence results of Vit B₁₂ deficiency and pernicious anaemia are likely to vary among the mixed population groups. Hence such studies need to be carried out in various regions and sectors of the country.

Acknowledgements

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References