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Study of symptoms and clinical features of Vitamin B12 deficiency

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ABSTRACT

Background: Vitamin B12 deficiency is a common nutritional disorder with diverse clinical manifestations affecting multiple organ systems. Owing to its varied presentation, the condition is frequently underrecognized, leading to delayed diagnosis and potentially irreversible complications. This study was undertaken to evaluate the symptom profile and clinical features of vitamin B12 deficiency and to examine their association with biochemical severity.

Materials and Methods: This hospital-based, cross-sectional observational study was conducted in a tertiary care center and included 160 adult patients with biochemically confirmed vitamin B12 deficiency. Detailed clinical history, physical examination, and laboratory investigations were performed using a structured proforma. Patients were categorized based on serum vitamin B12 levels, and the distribution of symptoms, clinical signs, and hematological parameters was analyzed. The association between serum vitamin B12 levels and neurological manifestations was assessed using chi square test.

Results: The study population predominantly comprised middle-aged adults, with a higher proportion of males and a majority following a vegetarian diet. Constitutional symptoms such as fatigue and generalized weakness were the most frequently reported complaints. Neurological manifestations, particularly sensory symptoms, were commonly observed, while gait disturbances and cognitive symptoms were less frequent. Pallor was the most prevalent clinical sign, and hematological evaluation revealed features consistent with macrocytic anemia. A significant association was observed between lower serum vitamin B12 levels and the presence of neurological manifestations, with a progressive increase in neurological involvement as the severity of deficiency increased.

Conclusion: Vitamin B12 deficiency is associated with varied and often nonspecific clinical manifestations, with neurological involvement showing a strong relationship to the severity of biochemical deficiency. Early clinical suspicion supported by laboratory confirmation is crucial to facilitate timely intervention and prevent long-term complications.

Keywords*: Vitamin B12 deficiency; Clinical features; Neurological manifestations; Macrocytic anemia; Nutritional deficiency*

INTRODUCTION

Vitamin B12 (cobalamin) is essential for DNA synthesis and normal neurological function, and deficiency can affect the hematopoietic system as well as the peripheral and central nervous systems [1–3]. Clinically, the disorder is notable for its protean presentation: patients may report vague, nonspecific symptoms (e.g., fatigue, reduced exercise tolerance) or present with overt hematological abnormalities, neuropsychiatric symptoms, or both [2,4]. Importantly, neurological involvement may occur even in the absence of striking anemia, and delayed recognition can be associated with incomplete neurological recovery despite replacement therapy [2–4].

The etiological spectrum of vitamin B12 deficiency varies by geography and population. In settings where intake of animal-source foods is limited, dietary insufficiency and related risk patterns contribute substantially to deficiency, whereas malabsorption and autoimmune causes (including pernicious anemia) remain important contributors across populations [2,4,5]. In India, adherence to vegetarian dietary practices and other region-specific factors have repeatedly been highlighted as clinically relevant in hospital-based cohorts, reinforcing the need for context-specific clinical suspicion and evaluation strategies [6].

From a clinical standpoint, vitamin B12 deficiency is frequently encountered at the interface of medicine, neurology, and hematology. Neurological manifestations such as peripheral neuropathy, myelopathy, gait impairment, and cognitive or affective changes are well-described, reflecting the vitamin's role in myelin integrity and one-carbon metabolism [3,4]. Concurrently, hematological manifestations typically include macrocytosis and megaloblastic anemia, which may prompt evaluation but are not universally present at first contact [2,5].

Despite being a treatable condition, vitamin B12 deficiency may remain underdiagnosed because symptoms can be subtle, overlap with other common disorders, and evolve over time [1,2,5]. A structured description of symptom patterns and examination findings within a defined clinical cohort can therefore support earlier recognition and targeted testing, particularly in populations with prevalent dietary or medication-related risk factors [4,6]. Accordingly, the present study aimed to characterize the symptom profile and clinical features among adults with biochemically confirmed vitamin B12 deficiency and to examine the relationship between biochemical severity and neurological involvement.

MATERIAL AND METHODS

Study Design and Setting: This was a hospital-based, observational, cross-sectional study conducted at a tertiary care teaching hospital in India. The study aimed to evaluate the spectrum of symptoms and clinical features associated with vitamin B12 deficiency among adult patients presenting to outpatient and inpatient services.

Study Population: Adult patients aged ≥18 years who attended the medicine outpatient department or were admitted to medical wards during the study period and were found to have biochemical evidence of vitamin B12 deficiency were considered for inclusion.

Sample Size: The sample size was calculated based on an expected prevalence of neurological manifestations among patients with vitamin B12 deficiency of approximately 40%, as reported in previous hospital-based studies, with a 95% confidence level and an absolute precision of 8%. Using the standard formula for sample size estimation in cross-sectional studies, the minimum required sample size was calculated to be 144. To account for possible incomplete data and exclusions, a total of 160 patients were enrolled in the study.

Inclusion Criteria

- Age ≥18 years
- Serum vitamin B12 level below the laboratory reference range (<200 pg/mL)
- Willingness to participate and provide written informed consent

Exclusion Criteria

- Patients already receiving vitamin B12 supplementation within the preceding three months
- Pregnant or lactating women
- Patients with known chronic liver disease, chronic kidney disease, malignancy, or autoimmune disorders
- Patients with acute infections or critical illness at the time of evaluation
- Patients with documented folate deficiency without concomitant vitamin B12 deficiency

Data Collection: After obtaining informed consent, detailed clinical evaluation was performed using a predesigned and structured proforma. Demographic data including age, sex, dietary habits (vegetarian or mixed diet), and relevant medical history were recorded.

A comprehensive assessment of symptoms was carried out, focusing on:

- General symptoms such as fatigue, weakness, and weight loss
- Gastrointestinal symptoms including anorexia, nausea, and diarrhea
- Neurological symptoms such as paresthesia, numbness, gait disturbances, memory impairment, and behavioral changes
- Hematological symptoms including breathlessness and palpitations

Clinical examination included general physical examination with emphasis on pallor, icterus, glossitis, and hyperpigmentation, followed by a detailed neurological examination assessing sensory deficits, reflexes, muscle strength, coordination, and gait.

Laboratory Investigations: Venous blood samples were collected under aseptic precautions. Laboratory investigations included complete blood count, peripheral blood smear examination, and serum vitamin B12 estimation. Serum vitamin

B12 levels were measured using a chemiluminescence immunoassay method, as per standard laboratory protocol. Additional investigations such as serum folate levels, fasting blood glucose, thyroid function tests, and liver and renal function tests were performed where clinically indicated to exclude confounding conditions.

Outcome Measures: The primary outcome measure was the prevalence and pattern of clinical symptoms and signs associated with vitamin B12 deficiency. Secondary outcomes included the association between clinical manifestations and hematological or neurological findings.

Statistical Analysis: Data were entered into a spreadsheet and analyzed using standard statistical software. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Associations between variables were analyzed using chi square test, with a p-value <0.05 considered statistically significant.

RESULTS

A total of 160 patients with confirmed vitamin B12 deficiency were included in the analysis. The study population comprised adults across a wide age range, with representation from all predefined age groups and a predominance of middle-aged individuals. Male participants constituted a higher proportion than females, and a majority of patients reported a vegetarian dietary pattern (Table 1).

The clinical presentation of vitamin B12 deficiency was heterogeneous. General constitutional symptoms were common, with most patients reporting nonspecific complaints such as fatigue and generalized weakness. Neurological symptoms formed a substantial component of the clinical spectrum, particularly sensory disturbances, while higher cortical and gait-related symptoms were observed in a smaller subset. Gastrointestinal and cardiopulmonary symptoms were also noted, reflecting the multisystem involvement associated with vitamin B12 deficiency (Table 2).

On physical examination, pallor was the most frequently observed sign, consistent with hematological involvement. Mucocutaneous manifestations such as glossitis and hyperpigmentation were noted in a considerable proportion of patients. Objective neurological signs, including impaired vibration sense, reduced deep tendon reflexes, and gait abnormalities, were identified in a subset of patients, corroborating the symptom profile reported at presentation (Table 3).

Hematological evaluation demonstrated features suggestive of macrocytic anemia, with reduced hemoglobin levels and elevated mean corpuscular volume. Other hematological indices, including total leukocyte and platelet counts, were largely within acceptable ranges, indicating selective involvement of erythroid parameters in most cases (Table 4).

Based on serum vitamin B12 concentrations, patients were categorized into three severity groups. A substantial proportion of participants had moderate deficiency, while nearly one-third exhibited severe deficiency. Mild deficiency constituted the remaining group, indicating that a wide spectrum of biochemical severity was represented in the study cohort (Table 5).

Neurological manifestations showed a clear association with the severity of vitamin B12 deficiency. Patients with lower serum vitamin B12 levels demonstrated a higher likelihood of neurological involvement, whereas those with relatively higher levels were more likely to be neurologically asymptomatic. This gradient suggests a dose–response relationship between biochemical deficiency and neurological expression (Table 6).

Table 1. Demographic Characteristics of Study Participants (n = 160)

Variable	Frequency (n)	Percentage (%)
Age group (years)		
18–30	32	20.0
31–45	46	28.8
46–60	52	32.5
>60	30	18.7
Sex		
Male	94	58.8
Female	66	41.2
Dietary pattern		
Vegetarian	102	63.8
Mixed diet	58	36.2

Table 2. Distribution of Presenting Symptoms among Patients with Vitamin B12 Deficiency

Symptom	Number of patients (n)	Percentage (%)
Fatigue / easy fatigability	118	73.8
Generalized weakness	104	65.0
Paresthesia (tingling/numbness)	92	57.5

Gait disturbance	38	23.8
Memory impairment	34	21.3
Anorexia	56	35.0
Weight loss	42	26.3
Breathlessness	48	30.0
Palpitations	36	22.5

Table 3. Clinical Signs Observed on Physical Examination

Clinical finding	Number of patients (n)	Percentage (%)
Pallor	110	68.8
Glossitis	52	32.5
Hyperpigmentation	44	27.5
Icterus	18	11.3
Impaired vibration sense	58	36.3
Reduced ankle reflexes	46	28.8
Ataxic gait	30	18.8

Table 4. Hematological Parameters of Study Participants

Parameter	Mean ± SD
Hemoglobin (g/dL)	9.8 ± 2.1
Mean corpuscular volume (fL)	104.6 ± 12.8
Total leukocyte count (cells/mm³)	6,480 ± 1,420
Platelet count (×10⁵/mm³)	1.82 ± 0.56

Table 5. Severity of Vitamin B12 Deficiency Based on Serum Levels

Serum vitamin B12 level (pg/mL)	Number of patients (n)	Percentage (%)
<100	48	30.0
100–149	62	38.8
150–199	50	31.2

Table 6. Association between Serum Vitamin B12 Levels and Neurological Manifestations

Serum vitamin B12 level (pg/mL)	Patients with neurological manifestations n (%)	Patients without neurological manifestations n (%)	Total (n)
<100	38 (79.2)	10 (20.8)	48
100–149	36 (58.1)	26 (41.9)	62
150–199	18 (36.0)	32 (64.0)	50
Total	**92 (57.5)**	**68 (42.5)**	**160**

DISCUSSION

In this hospital-based cohort of adults with biochemically confirmed vitamin B12 deficiency, the clinical picture was dominated by nonspecific constitutional complaints alongside a substantial burden of neurological symptoms and signs. This overall pattern is consistent with contemporary clinical observations that vitamin B12 deficiency frequently presents to general medicine with mixed systemic and neuro-hematological features rather than a single “classic” phenotype, which can contribute to delayed recognition in routine care [7].

A notable contextual finding was the predominance of vegetarian dietary practice among affected individuals, supporting dietary insufficiency as a key contributing factor in similar settings. Evidence from plant-predominant diet literature indicates that low or absent intake of animal-source foods, without reliable fortification or supplementation, is a well-established pathway to deficiency and related morbidity, including megaloblastic anemia and neuropathy [8,9]. In addition, systematic syntheses using biomarker-based definitions suggest that functional vitamin B12 deficiency is a meaningful risk in unsupplemented vegan populations and can occur across plant-based dietary patterns when intake is persistently low [9]. Together, these data reinforce the clinical need to actively elicit dietary history and to maintain a low threshold for testing in symptomatic patients from at-risk dietary groups [8,9].

The hematological profile in the present study demonstrated macrocytic indices alongside anemia, aligning with the expected megaloblastic physiology of cobalamin deficiency. However, recent hospital-based work has emphasized that reliance on macrocytosis alone may be misleading because normocytic presentations can also be common, particularly when deficiency coexists with other nutritional or inflammatory states [7]. Practically, these insights support a symptom- and risk-based diagnostic approach rather than one anchored solely to red cell indices, especially in resource-constrained environments where patients may present late or with multiple overlapping etiologies [7].

Neurological involvement showed a clear gradient across biochemical severity categories, with greater neurological burden in those with lower serum vitamin B12 levels. This relationship is biologically plausible because cobalamin is essential for myelin maintenance and one-carbon metabolism, and progressive deficiency increases vulnerability to neuropathy and myelopathy. Contemporary reviews of subacute combined degeneration describe early sensory symptoms and gait-related manifestations as typical clinical entry points, with risk of progression when diagnosis and replacement are delayed [10]. Furthermore, recent neurocognitive reviews position vitamin B12 deficiency as a modifiable contributor to cognitive symptoms through mechanisms that include disrupted myelin integrity and altered homocysteine metabolism [11]. While the present study did not incorporate advanced biomarkers or neuroimaging, the observed clinical gradient supports the concept that greater biochemical depletion is more likely to be clinically expressed in the nervous system.

Beyond diet, medication-associated deficiency remains a critical contemporary consideration. Large database analyses and cohort studies have linked long-term metformin exposure to increased risk of vitamin B12 deficiency and higher neuropathy burden, supporting routine consideration of B12 assessment in individuals with prolonged use or neuropathic symptoms [12,13]. Similarly, a systematic review and meta-analysis of proton pump inhibitor exposure reported a small increase in odds of deficiency among users, albeit with heterogeneity and modest effect size—suggesting that chronic PPI therapy may be one contributor among several rather than a standalone explanation [14]. Taken together, these data support integrating diet and medication history into bedside assessment and case-finding strategies.

From a management perspective, route of replacement has practical implications for follow-up and adherence. A recent network meta-analysis concluded that intramuscular, oral, and sublingual vitamin B12 can all effectively raise vitamin B12 levels without clinically meaningful differences between routes, which is relevant in settings where injection access or acceptance is limited [15]. Although therapeutic outcomes were not evaluated in this study, this evidence supports flexible, patient-centered replacement strategies once deficiency is identified, with route selection tailored to severity, suspected malabsorption, and feasibility [15].

This study has limitations typical of single-center observational designs, including the absence of confirmatory functional biomarkers (e.g., methylmalonic acid or homocysteine), limited etiological work-up in all patients, and potential referral bias. Nonetheless, the structured documentation of symptom patterns, examination findings, and the observed severity–neurology gradient provides clinically actionable information and emphasizes the need for early identification—particularly in individuals with dietary risk patterns and those exposed to medications associated with reduced cobalamin status [8,12–14].

CONCLUSION

Vitamin B12 deficiency presents with a broad spectrum of clinical manifestations, encompassing constitutional, hematological, neurological, and mucocutaneous features. The findings of this study highlight that neurological involvement is common and shows a clear relationship with the severity of biochemical deficiency, underscoring the importance of early recognition and evaluation. Given the predominance of nonspecific symptoms and the high proportion of individuals with dietary risk factors, vitamin B12 deficiency may remain underdiagnosed in routine clinical practice. Timely identification through clinical assessment supported by laboratory evaluation is essential to prevent potentially irreversible neurological complications and to improve overall patient outcomes.

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