Original Article

Vitamin B12 deficiency in northern India tertiary care: Prevalence, risk factors and clinical characteristics

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Abstract

Background: Vitamin B12 deficiency leads to a diversity of symptoms and affects many systems. It is often overlooked or sometimes even misdiagnosed in clinical practice. **Aims and Objectives:** The purposes of this study were to report the prevalence of vitamin B12 deficiency, the spectrum of clinical features and to draw attention to the possibility of rare hidden characteristics. **Materials and Methods:** This study was a multicenter, retrospective, and prospective conducted at a tertiary care teaching hospital and multispecialty hospital. All cases of vitamin B12 deficiency of either sex or age attending the Medicine Department were enrolled in this study from Aug 2015 to Dec 2020. Parenteral vitamin B12 was given, and cases were evaluated for the response on follow-up for more than three months. **Results:** Of 220 cases, 52.27% were males. Maximum cases were reported from the age group 50 to 65 years (27.27%) and belonged to urban areas (59.1%). The majority were strict vegetarian (86.36%). Among comorbidities, diabetes (20.91%) followed by malabsorption (10.45%) were most common. The cutaneous manifestations were revealed at 38.18%. The most frequent neurological manifestation was paraesthesia (98.18%). Head heaviness/ache was the most frequent (95%) psychiatric manifestation. Anemia was revealed in 87.73% of cases with 88.64% macrocytosis. Axonal sensorimotor (52.63%) neuropathy was a prevalent finding of NCV study. **Conclusions:** A high index of clinical suspicion is needed in cases with vague manifestations, especially in the pure vegetarian population. Early recognition can prevent further damage as most of its related disorders are generally reversible with treatment.

Keywords: Chronic fatigue, headache, hyperpigmentation, pancytopenia, paraesthesia, pure vegetarian diet

Introduction

Vitamin deficiencies are well known to cause various impacts on human health. Vitamin B12 is one of them which has a vital role in DNA synthesis. It is well recognized that cyanocobalamin deficiency is associated with hematologic, neurologic, psychiatric, cutaneous, gastrointestinal, and cardiovascular disorders, and its deficiency is reported in all age groups.[1] Vitamin B12 deficiency is not scarce in India as a majority of the population is vegetarian.[2] Vitamin B12 deficiency usually presents in the usual way but sometimes very difficult to suspect due to atypical manifestation.[3] Many times the patient was not searched for vitamin deficiency, causing more faltering. This study described the experience of patients with vitamin B12 deficiency presenting a range of clinical manifestations and the pitfalls of diagnosis and treatment.

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Received: 06-04-2021 **Revised:** 05-07-2021
Accepted: 13-07-2021 **Published:** 30-06-2022

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_650_21

Materials and Methods

Design and setting

This study was a multicentric, retrospective, and prospective conducted at King George Medical University (KGMU), Lucknow study from Aug 2015 to July 2016, Heritage institute

How to cite this article: Singh J, Dinkar A, Gupta P, Atam V. Vitamin B12 deficiency in northern India tertiary care: Prevalence, risk factors and clinical characteristics. J Family Med Prim Care 2022;11:2381-8.

of medical sciences (HIMS), Varanasi from Aug 2016 to July 2017, Popular Multispecialty hospital, Varanasi from Aug 2017 to Dec 2019 and Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh from Sept 2020 to Dec 2020.

Study population and methodology

Clinically suspected cases of either sex or age attending the Medicine Department were investigated for Vitamin B12 deficiency. Of 220 confirmed cases, 30 cases from KGMU, 20 cases from HIMS, 154 cases from Popular hospital and 16 cases from IMS, BHU were enrolled in the study. All cases were examined thoroughly for detailed histories, demographics, clinical features, and associated comorbidities. Vitamin B12 and blood routines were estimated of all suspected cases in the outdoor and indoor patient departments. Based on clinical assessment, other relevant investigations such as neuroimaging and electrophysiological studies were performed on selected cases. Patients having normal vitamin B12 level but clinically shady underwent bone marrow examination. Megaloblastic changes in bone marrow were ruled out for other causes. The diagnosis was established by one or both of the following (I) low serum vitamin B12 levels (<145 pg/mL) assessed by Chemiluminescence (CLIA) method. (II) Bone marrow aspiration showing megaloblastic changes. Mini-mental status examination (MMSE) was used to test dementia.

Intramuscular B12 injections (cyanocobalamin 1000 micrograms) were given daily for 1 week, followed by once a week for 4 weeks and thereafter monthly for a long time. Evaluation for response in terms of clinical examination, laboratory parameters, and other appropriate investigations were done on follow-up accordingly. Among 220 cases, 209 (95%) cases had low serum vitamin B12 levels, and 11 (5%) cases were diagnosed by bone marrow findings. Patients not willing for consent and those having folate deficiency were excluded from the study.

Ethical issue

Ethical Committee approval was taken. Informed or/and written consents were obtained. Though, we caution not to disclose the identity of the patient in any form.

Results

Of 220 cases, males were 115 (52.27%) with male and female ratio of 1.1. Maximum cases 60 (27.27%) were reported from the age group 50 to 65 years, and the lowest cases 33 (15%) from age less than 20 years. Male cases were a maximum of 39 (17.72%) in the age group 50 to 65 years, and females were dominant 36 (16.36%) in the age group 35-50 years.

The highest cases, 130 (59.1%), were from the urban areas. In which males were dominant in urban areas with 85 (38.64%) and females were highest in a rural area with 60 (27.27%).

A bulk of cases 190 (86.36%) were pure vegetarians. In which, females 99 (45%) were more prevalent than males 91 (41.36%).

Drug history of cases revealed as 40 (18.18%) cases were taking different PPIs (Proton pump inhibitors), and 21 (9.54%) cases were on Histamine H2 blocker. Overall, 61 (27.73%) cases were using different PPIs/Histamine H2 blockers for more than one year of duration.

Among comorbidities, most frequent was diabetes on metformin with 46 (20.91%) followed by chronic diarrhea/malabsorption 23 (10.45%), dyspepsia 22 (10%), and hypothyroidism with 19 (8.63%) cases [Table 1].

There was a wide range of clinical features. In cutaneous manifestations, the most common were pale skin in 84 (38.18%), glossitis in 78 (35.45%), and hyperpigmentation of skin 37 (16.81%). Vitiligo was present in 6 (2.73%) cases, and 1 case was recovered fully while 4 cases do not respond to therapy.

The neurological manifestations were most prevalent among cases with the most frequent paresthesia as 216 (98.18%) followed by impaired vibratory sense 162 (73.63%), position sense 111 (50.45%) and touch or pain sense 93 (42.27%), respectively.

The common psychiatric manifestations of vitamin B12 deficiency were as head heaviness/ache 209 (95%), anxiety 184 (83.63%), and irritability 113 (51.36%). Apart from these symptoms, chronic fatigue was revealed in 180 (81.82%) cases. The detail of clinical features is in Table 2.

Anemia was revealed most prevalent finding with 193 (87.73%) cases (mean 9.14 gm/dL), in which severe anemia was present in 51 (23.18%) cases (mean 5.6 gm/dL). Macrocytosis (MCV >100 fL) was found in 195 (88.64%) cases with 20% macro-ovalocytes. Hypersegmented polymorphs were seen in 132 (60%) cases [Figure 1]. Pancytopenia was diagnosed in 28 (12.73%) cases. The mean of macrocytosis, leucopenia, and thrombocytopenia was calculated as 108.8Fl, 2693/cumm, and 106000/cumm, respectively. Serum LDH was investigated in 164 cases, and 138 (84.15%) cases had increased value with a mean of 983 U/L. Deranged LFT was observed in 22 (10%) cases. Hypoalbuminemia was prevalent in 21 (9.55%) with a mean of 2.73 gm/dL [Table 3]. Bone marrow examination of 52 cases showed megaloblastic changes in 40 (76.92%) cases [Figure 2]. Neuroimaging (CT

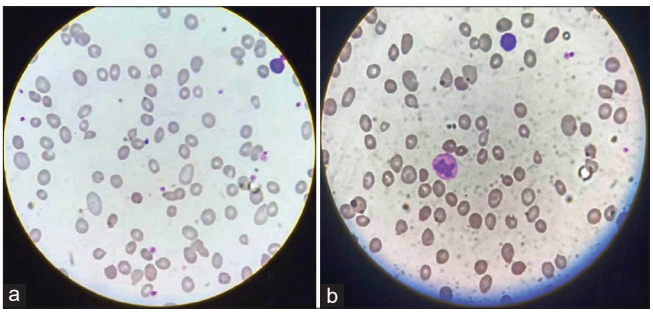

Figure 1: Peripheral blood smear (Leishman stain ×100) showing (a) Macro-ovalocytes (b) Hypersegmented neutrophil and macro-ovalocytes

Head/MRI Brain was done in 161 cases, of the 49.07%) was normal. The most common finding was cerebral atrophy 35 (21.74%), followed by lacunar infarcts in 11.8% of cases. The nerve conduction velocity (NCV) studies were performed in 38 cases in which axonal sensory-motor neuropathy was detected, most common with 22 (57.89%) cases. Findings are summarized in Table 4.

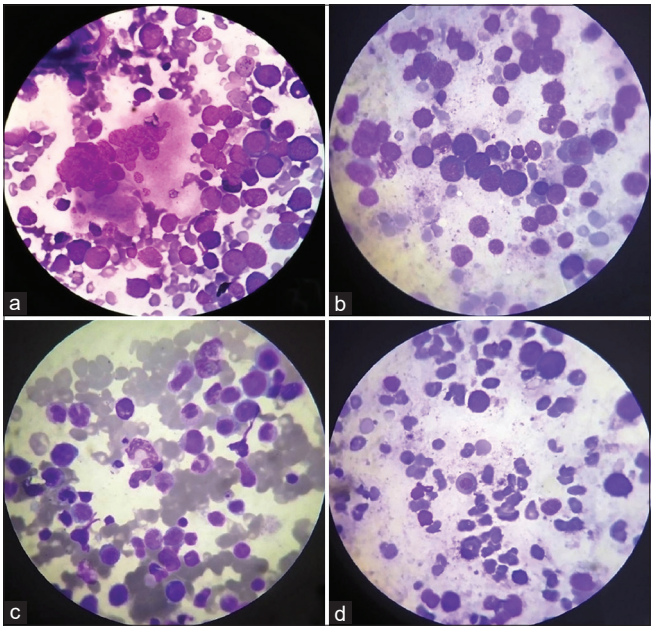

Figure 2: Bone marrow examination (Giemsa stain × 100) (a) Erythroid hyperplasia with hyperlobulated megakaryocytes (b) Dyserytrhopoeisis with megaloblasts having sieve-like nucleus (c) Giant band forms (d) Megaloblast showing nucleocytoplasmic asynchrony follow-up

Discussion

Risk factors for vitamin B12 deficiency

The prevalence of Vitamin B12 deficiency is reported 3 to 5% in the general population while 5 to 20% among older people of more than 65 years.[4,5] The result of the age distribution in this study was quite remarkable. Prevalence was an increasing trend up to age 65 years with maxima of 27.27%. Above the age of 65 years, the prevalence was low as 16.36%. Interestingly, vitamin B2 deficiency was more common in females up to 50 years, whereas males were prevalent after the age of 50 years. An Indian study also had shown maximum cases from the age group of 31 to 50 years.[6]

The urban population was more vitamin B12 deficient with 59.1% cases, which favors a previous study of south India.[6] Further description of cases demonstrated males were dominant in urban while females were common in rural areas.

Table 1: Demographic characteristics and comorbidities of cases (*n*=220)

Demographics	Vitamin B12 deficiency		Total
	Male	Female	
Age			
<20	15 (6.82%)	18 (8.18%)	33 (15%)
20-35	18 (8.18%)	21 (9.54%)	39 (17.72%)
35-50	16 (7.27%)	36 (16.36%)	52 (23.63%)
50-65	39 (17.72%)	21 (9.54%)	60 (27.27%)
>65	27 (12.27%)	9 (4.09%)	36 (16.36%)
Residence			
Urban	85 (38.64%)	45 (20.45%)	130 (59.1%)
Rural	30 (13.63%)	60 (27.27%)	90 (40.91%)
Diet			
Pure veg diet	91 (41.36%)	99 (45%)	190 (86.36%)
Non veg diet	24 (10.91%)	6 (2.73%)	30 (13.64%)
Total	115 (52.27%)	105 (47.73%)	220
Drug history			
Proton pump inhibitor (use >1 year)	26 (11.82%)	14 (6.36%)	40 (18.18%)
Histamine H2 blocker (use >1 year)	13 (5.91%)	8 (3.63%)	21 (9.54%)
Total	39 (17.72%)	22 (10%)	61 (27.73%)
Comorbidities			
Diabetes on Metformin	34 (15.45%)	12 (5.45%)	46 (20.91%)
Malabsorption	16 (7.27%)	7 (3.18%)	23 (10.45%)
Dyspepsia	15 (6.82%)	7 (3.18%)	22 (10%)
Hypothyroidism	6 (2.72%)	13 (5.91%)	19 (8.63%)
Chronic alcoholism	15 (6.82%)	0	15 (6.82%)
Chronic kidney disease	9 (4.1%)	3 (1.36%)	12 (5.45%)
Hypertension	8 (3.63%)	2 (0.91%)	10 (4.54%)
Diabetes on insulin	6 (2.72%)	3 (1.36%)	9 (4.1%)
Hyperthyroidism	3 (1.36%)	0	3 (1.36%)

Table 2: Clinical characteristics of cases (*n*=220)

Clinical features	Response to cobalamine therapy			
	Total	Complete	Partial	No response
Mucocutaneous manifestations				
Pale skin	84 (38.18%)	76 (34.54%)	-	8 (3.63%)
Glossitis	78 (35.45%)	53 (24.1%)	-	4 (1.82%)
Hyperpigmentation	37 (16.81%)	28 (12.72%)	4 (1.82%)	5 (2.27%)
Hair changes	26 (11.81%)	18 (8.18%)	3 (1.36%)	5 (2.27%)
Stomatitis	13 (5.91%)	12 (5.45%)	-	1 (0.45%)
Jaundice	9 (4.1%)	9 (4.1%)	-	-
Vitiligo	6 (2.73%)	1 (0.45%)	1 (0.45%)	4 (1.82%)
Neurological manifestations				
Paraesthesia	216 (98.18%)	196 (89.1%)	11 (5%)	9 (4.1%)
Impaired vibratory sense	162 (73.63%)	77 (35%)	31 (14.1%)	54 (24.55%)
Impaired position sense	111 (50.45%)	94 (42.72%)	7 (3.18%)	10 (4.54%)
Impaired touch or pain sense	93 (42.27%)	73 (33.18%)	5 (2.27%)	15 (6.81%)
Decreased reflexes	36 (16.36%)	25 (11.36%)	10 (4.55%)	1 (0.45%)
Ataxia	24 (10.91%)	13 (5.91%)	6 (2.73%)	5 (2.27%)
Muscle cramps	23 (10.45%)	11 (5%)	7 (3.18%)	5 (2.27%)
Increased reflexes	16 (7.27%)	11 (5%)	-	5 (2.27%)
Urinary incontinence	13 (5.91%)	8 (3.64%)	3 (1.36%)	2 (0.91%)
Obtundation	13 (5.91%)	7 (3.18%)	5 (2.27%)	1 (0.45%)
Impaired taste sense	9 (4.1%)	8 (3.64%)	-	1 (0.45%)
Babinski's signs	9 (4.1%)	9 (4.1%)	-	-
Spasticity	2 (0.91%)	1 (0.45%)	-	-
Seizure	1 (0.45%)	1 (0.45%)	-	-
Impaired smell sense	1 (0.45%)	1 (0.45%)	-	-
Psychiatric manifestations				
Head heaviness/ache	209 (95%)	190 (86.36%)	2 (0.91%)	-
Anxiety	184 (83.63%)	162 (73.64%)	12 (5.45%)	10 (4.55%)
Irritability	113 (51.36%)	87 (39.55%)	14 (6.36%)	12 (5.45%)
Lack of interest	77 (35%)	57 (25.91%)	12 (5.45%)	8 (3.64%)
Cognitive impairment	70 (31.82%)	61 (27.73%)	6 (2.73%)	3 (1.36%)
Mood changes	69 (31.36%)	33 (15%)	23 (10.45%)	13 (5.91%)
Memory loss	66 (30%)	35 (15.91%)	10 (4.55%)	21 (9.55%)
Depression (mild)	14 (6.36%)	14 (6.36%)	-	-
Erectile dysfunction	12 (5.45%)	7 (3.18%)	2 (0.91%)	3 (1.36%)
Hematological related/others manifestations				
Chronic fatigue	180 (81.82%)	171 (77.73%)	11 (5%)	9 (4.1%)
Breathlessness	38 (17.27%)	38 (17.27%)	-	-
Dizziness/Vertigo	50 (22.73%)	50 (22.73%)	-	-

Vitamin B12 is synthesized by bacteria, and its root source is the consumption of animal-derived products such as meat, egg, and dairy products, but not in plant origin products.[7] The basic causes of vitamin B12 deficiency are illustrated in Table 5.[8] Some studies revealed the major cause of vitamin deficiency is the inadequate consumption of animal source foods and pernicious anemia in the young population, while malabsorption in part of the gut due to gastric atrophy may be the leading cause of the deficiency state in older patients.[5,9]

This study did not find such association and revealed 86.36% pure vegetarian population distributed in all age groups. The prevalence of vitamin B12 deficiency conducted in South India reported a strict vegetarian as 60%.[6] Most studies from different regions of India showed a strong association of a strict vegetarian diet to vitamin B12 deficiency. Vitamin B12 deficiency is still prevalent in the developing world due to adherence to the diet containing more plant-derived products.[7] Particularly in India, the bulk of vitamin B12 deficiency is pure vegetarians. Besides economic constraints in India, various sections of society and religions followed pure vegetarian diets.

One more thing to emphasize on self-medication is common in India, and the study traced 27.73% of cases who were taking PPI/H2 blockers for more than one year. This is another challenging issue contributing to the deficiency of vitamin B12. A previous study had supported that the use of gastric acid inhibitors is significantly associated with vitamin B12 deficiency.[10] Conversely, a study conducting on 250 adult subjects using PPIs for 12 months did not lead to clinically significant vitamin B12 deficiency.[11]

Table 3: Laboratory parameters of cases (*n*=220)

Parameters on the first visit	Mean	Cases with deranged value (%)
Anemia (Hb 7-12 gm/dL)	9.145	142 (64.55%)
Anemia (Hb <7 gm/dL)	5.6	51 (23.18%)
Macrocytosis (MCV >100 fL)	108.8	195 (88.64%)
Macro ovalocytes	-	44 (20%)
Hypersegmented polymorphs	-	132 (60%)
Basophilic stippling	-	12 (5.45%)
Leucopenia (TLC <4000/cumm)	2693	31 (14.1%)
Throbocytopnia (PC <150000/cumm)	106000	16 (7.27%)
Pancytopenia	-	28 (12.73%)
Thrombocytosis (PC >440000/cumm)	514000	5 (2.27%)
Increased LDH (>414 U/L) (n=164)	983	138 (84.15%)
Increased Bilirubin (>1.2 mg/dL)	2.62	10 (4.55%)
SGPT (>40 U/L)	127.5	22 (10%)
SGOT (>40/L)	95.5	18 (8.18%)
Hypoproteinemia (<6.4 g/dL)	5.57	10 (4.55%)
Hypoalbuminemia (<3.5 g/dL)	2.73	21 (9.55%)

Hb: Hemoglobin, MCV: Mean corpuscular volume, TLC: Total leukocyte count, PC: Platelet counts, LDH: Lactate dehydrogenase, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase

Table 4: Bone marrow examination, neuroimaging and nerve conduction velocity studies of cases

Investigations and findings	Cases	(%)
Bone marrow examination (*n*=52)		
Normal	12	23.08
Megaloblastic changes	40	76.92
Findings of CT Head/MRI Brain (*n*=161)		
Normal	79	49.07
Cerebral atrophy	35	21.74
Bilateral white matter lesions in the corona radiate and centrum ovale	8	4.97
Bilateral white matter lesions in the periventricular area	12	7.45
Lacunar infarcts	19	11.8
Diffuse cerebral atrophy with lesions in the bilateral cerebellar cortex	8	4.97
Nerve conduction velocity study (*n*=38)		
Normal	6	15.79
Axonal sensorimotor neuropathy	22	57.89
Demyelinating sensorimotor neuropathy	2	5.26
Mixed type (sensorimotor and demyelinating) neuropathy	8	21.05

After a purely vegetarian diet and drug misuse, comorbidities are confluence to factors imparting vitamin B12 deficiency. The approximation of comorbidities encountered in the study is depicted in Table 1, as the sometimes single individual was suffering from one or more disorders. Here, the study revealed 20.91% of cases of diabetes who were on metformin ± other antidiabetic drugs. The mean duration of diabetes was 6.5 years. Metformin itself is a common cause of vitamin B12 deficiency among drugs.[12] Therefore, patients on metformin for a long time need close observation for vitamin B12 deficiency or call for B12 supplements in more risk patients.

In contrast to India, the diet in developed countries is cobalamin-rich animal-derived food thus, vitamin B12 deficiency is relatively rare, and malabsorption remains the most common cause of cobalamin deficiency.[13] In our scenario, malabsorption was reported on the fourth stance with 10.45% cases inducing vitamin B12 deficiency. The decreasing order of commonly traced potential factors leading to malabsorption was subclinical, clinical, or treated ileocecal tuberculosis, chronic pancreatitis, hepatobiliary dysfunction, ileal resections due to different reasons Worm infestations, Celiac disease, and Crohn's disease. One old aged female was found to have radiation enteritis.

Dyspepsia due to many reasons was observed in 10% of cases. Gastritis, peptic ulcers, *Helicobacter pylori* infection, irritable bowel syndrome, gastroesophageal reflux, and hiatus hernia were crucial disorders causing dyspepsia.

The present study found that 8.63% of vitamin B12 deficiency patients were already established hypothyroidism. Surprisingly, a study conducted in Karachi, Pakistan, revealed a high (approximately 40%) prevalence of B12 deficiency in hypothyroid patients.[14] Hypothyroidism can cause vitamin B12 deficiency by various factors such as inadequate intake or altered intestinal absorption due to sluggish bowel motility, bowel wall edema and bacterial overgrowth and, antibodies to gastric parietal cells in autoimmune etiology.[14] In our setting, of 19 cases, 17 were strict vegetarians. Therefore, diet and hypothyroidism both may reason for the deficiency of vitamin B12. On the other hand, 3 (1.3%) cases of vitamin B12 deficiency had hyperthyroidism, and all patients had chronic diarrhea, which may be the probable cause in our case.

Chronic alcoholism is known to decrease the absorption of zinc, B vitamins, notably thiamine, folate, and vitamin B12 but def of vitamin B12 deficiency is rare. Though, there were 6.82% of cases of chronic alcohol abuse in this study.[15]

Cutaneous manifestations

B12 deficiency is associated with cutaneous and mucosal hyperpigmentation, vitiligo, angular stomatitis, and hair changes.[1,2] The deep brown or brownish-black hyperpigmentation predominantly over the extremities (especially the knuckles, periungum, palmar creases, and soles) and oral mucosa is characteristic of vitamin B12 deficiency.[2,5] Sometimes, nail changes and premature graying of hair and accentuation of pigmentation on the pressure points such as elbows, malleoli, and knees have also been reported.[2] The possible pathophysiology of hyperpigmentation is (I) vitamin B12 deficiency decreases the reduced glutathione level, which increases the tyrosinase activity and leads to increased melanogenesis. (II) The fault in the melanin transfer between melanocytes and keratinocytes, resulting in pigmentary incontinence, may attribute to hyperpigmentation.[5] (III) it is also proposed that vitamin B12 deficiency is associated with increased biopterin levels which increase hydroxylated phenylalanine and thus result in hyperpigmentation.[2]

Table 5: Various risk factors causing vitamin B12 deficiency

Causes
Genetic
Transcobalamin II deficiency
Inadequate intake
Alcohol abuse, Patients older than 75 years, Vegans or strict vegetarians (including exclusively breastfed infants of vegetarian/vegan mothers)
Decreased ileal absorption
Ileal resection, Crohn disease, Tapeworm infection
Decreased intrinsic factor
Atrophic gastritis, Pernicious anemia, Postgastrectomy syndrome (includes Roux-en-Y gastric bypass)
Drugs
Histamine H2 blocker (use >1 year), Proton pump inhibitor (use >1 year), Metformin (use >4 months)

This study reported pale skin (38.18%) as the most common mucocutaneous manifestation.

Other manifestations were glossitis (35.45%), hyperpigmentation (16.81%), hair changes (11.81%), stomatitis (5.91%) and vitiligo (2.73%). These findings were near to Aaron *et al.*[6] as glossitis (31%), skin hyperpigmentation (19%), hair changes (9%), angular stomatitis (8%)%), and vitiligo (3%). These mucocutaneous manifestations are important clues to evaluate further for vitamin B12 deficiency.

Neurologic manifestations

The commonly encountered clinical features are paraesthesia in hands and feet, muscle cramps, dizziness, cognitive disturbances, ataxia, and erectile dysfunction, fatigue, and depression,[16] subacute combined degeneration of cord, orthostatic hypotension, optic atrophy, and dementia.[5]

Subacute combined degeneration of the cord is common and begins with paraesthesia of feet and fingers. It is classically characterized by symmetric dysesthesia, disturbance of position sense, and spastic paraparesis or tetraparesis.[13]

In our setting, paraesthesia (98.18%) was observed as the most common finding with 50.45% of impaired position sense. Loss of vibratory sense and diminished proprioception is due to posterior column involvement followed by spastic ataxia due to the involvement of lateral and dorsal columns of the spinal cord.[17] Here, impaired vibratory sense and impaired touch or pain sense were 73.63% and 42.27%, respectively. The corticospinal tract is involved in more advanced cases and manifests with abnormal reflexes, motor impairment, and, ultimately, spastic paraparesis.[18] Diminished reflexes, increased reflexes, and extensor plantar reflexes were noted as 16.36%, 7.27%, and 4.1%, respectively.

Peripheral neuropathy is reported by up to 25% in patients with vitamin B12 deficiency.[13] The pathologic findings are revealed axonal degeneration with or without demyelination, reported as 76% axonal, and 24% demyelinating neuropathy in a review article.[13] Our findings of NCV performed in 38 cases were as axonal sensory-motor neuropathy 57.89%, demyelinating sensorimotor 5.26%, mixed type (sensorimotor and demyelinating) neuropathy 21.05%, which were belike to an Indian study.[6]

Another frequent neurological manifestation is dementia which commonly mimics Alzheimer's disease in clinical practice. A minority of cases with vitamin B12 deficiency exhibited somnolence, perversion of taste, smell and vision, and acute reversible extrapyramidal syndrome.[17] There were 9 cases of altered taste sensation, in which 8 cases return to normal taste on therapy. A young girl was on 4 antiepileptic drugs for recurrent seizures. She had normal brain imaging but severely vitamin B12 deficit. On vitamin B12 supplementation, she improved dramatically and tapered to one antiepileptic drug (carbamazepine). A similar case of recurrent seizure resulting from vitamin B12 deficiency, ameliorated to parenteral vitamin B12 therapy is reported earlier.[3] The most likely mechanism involved in epileptogenesis may be as cerebral neurons with destroyed myelin sheaths due to vitamin B12 deficiency are more susceptible to the excitatory effects of glutamate.[3]

Psychiatric manifestations

Head heaviness/ache (95%) and anxiety (83.63%) were the most frequent psychiatric features. Various psychiatric disturbances or autonomic signs (bladder and erectile dysfunction) can occur in vitamin B12 deficiency as this study reported urinary incontinence 5.91% and erectile dysfunction 5.45%.[13,17]

Most psychiatric features, including cognitive impairment, responded well to vitamin B 12 supplements except dementia. A retrospective study found that vitamin B12 therapy improves cognitive impairment but does not reverse dementia.[19] Here study refined that dementia of short duration and lesser degree reversed on treatment, in contrast to some previous studies.[6,19] Depression, apathy, irritability, dementia, catatonia, delirium, and hallucinations are well reported in the literature.[7] A study conducted on psychiatric inpatients had shown vitamin B12 deficiency in 4%–6% cases. Mild depression was reported in 6.36% of cases and recurred fully on B12 therapy.

Hematologic manifestations

These are increased mean corpuscular volume (MCV), macrocytic anemia, leukopenia, thrombocytopenia, thrombocytosis, and pancytopenia.[5,8]

Hematological abnormalities in present study were revealed as anemia (64.5%), severe anemia [Hb level <7 g/dL] (23.2%), leukopenia (14.1%), thrombocytopenia (7.27%), pancytopenia (12.7%) macrocytosis (88.64%) and hyperpigmented neutrophils (60%) as compared to a previous study of 201 patients with documented cobalamin deficiency showing anemia (37%),%), severe anemia [Hb levels <6 g/dL]

(2.5%), leukopenia (13.9%), thrombocytopenia (9.9%), pancytopenia (5%), macrocytosis (54%) and hyperpigmented neutrophils (32%).[20]

However, studies from the Western world, as well as China, had demonstrated macrocytic anemia in less than 20% of cases with low serum vitamin B12.[16]

Furthermore, macroovalocytes and hypersegmented neutrophils in peripheral blood smear were more specific to surmise vitamin B12 deficiency, also supported by a review article.[13]

Hepatic dysfunction was found in 10% of cases, which might be due to hemolysis. Inadequate nutrition was the most probable cause of mild hypoalbuminemia (9.55%) in the study. All hematological abnormalities were corrected with intramuscular cyanocobalamin treatment.

The well-known cause of macrocytic anemia and reversible bone marrow failure is vitamin B12 deficiency.[21] The various conditions causing macrocytic anemia are alcoholism, liver disease, hypothyroidism, drugs, vitamin B12, or folate deficiency. In this setting, diagnosis is frequently determined by clinical history and appropriate blood investigations.[21] Bone marrow aspiration/biopsy is generally not indicated in this scenario until severe pancytopenia to rule out other causes or normal serum vitamin B12 level.

Cases on vitamin B12 supplements before visit their referral centers can influence the serum B12 levels, and during vitamin B12 depletion, it falls first in the neuronal tissues, and much later, it reflected in the serum.[6] It may be rationality why 11.6% of normal MCV was reported. In this regard, the megaloblastic changes in bone marrow testify to vitamin B12 deficiency. It was a fact to consider bone marrow as a definite criterion for diagnosis. Though folate deficiency had megaloblastic bone marrow, therefore serum folic acid assay is mandatory for confirmation.[6] In a study, 28% of patients of B12 deficiency with neuropsychiatric abnormalities were without any change in the hematocrit values or increase in red cell MCV.[7]

One more clinical feature, chronic fatigue, was demonstrated in 81.82% of patients. It was due to either anemia or vitamin B12 deficiency, which was not clearly stood in our setting. Though, patients reported fatigue despite the absence of anemia in a previous study.[22] In last, this study explores the diversity of clinical presentations, the risk population, and how a parlous clinical condition can treat easily if the diagnosis is confirmed. Better understanding the clinical spectrum of Vitamin B12 deficiency is critical for Primary care clinicians and can also practice the results of the present study as a clinical aid to look for Vitamin B12 deficiency.

Conclusion

Vitamin B12 deficiency can manifest a variety of presentations. Early recognition of deficiency is paramount to avoid irreversible neurological damage. Therefore, a high suspicion must be exercised in cases presenting with cutaneous and/or neuropsychiatric symptoms, particularly among the pure vegetarians and the elderly population and those who are refractory to respective conventional treatment. Bone marrow smear is essential where complete hemogram and serum B12 level are normal.

Acknowledgements

We thank our junior residents for patient care and Jaitik Dinkar Singh and Jenika Dinkar Singh for their kind support.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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