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Review Article

A Review of 89 Published Case Studies of Vitamin B12 Deficiency

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Abstract

Vitamin B12 (B12) is an essential nutrient needed for proper nervous system function and for the metabolism of carbohydrate, protein, and fat. Deficiencies in B12 can lead to inefficient erythropoiesis and megaloblastic anemia. The purpose of this review is to examine published case studies on vitamin B12 deficiency in adults, including a report of B12 deficiency in regards to causes, clinical manifestations, treatment/outcomes, and biomarkers of B12 status. A total of 89 applicable case studies were reviewed. Causes of B12 deficiency reported included malnutrition, lack of intrinsic factor (IF) and/or malabsorption of protein-bound vitamin B12, general malabsorption, and competition for vitamin B12. Clinical manifestations of B12 deficiency included neurological, psychiatric, oral, dermatological, and rare signs and symptoms. The majority of cases reported B12 replacement therapy via intramuscular (IM) administration. Additionally, parenteral and oral administration methods were utilized. Biomarkers of B12 status reported included serum B12 levels, mean corpuscular volume (MCV), and serum homocysteine. Serum methylmalonic acid (MMA) was also utilized in a small number of cases.

INTRODUCTION

Vitamin B12 (B12) is classified as a water-soluble vitamin, and is distinctive among all vitamins due to its large size, complexity, and that it contains the metal ion cobalt [1]. It is necessary for appropriate nervous system function and for the metabolism of carbohydrate, protein, and fat. Deficiencies in B12 can lead to inefficient erythropoiesis and megaloblastic anemia [2]. Furthermore, neurological disorders such as neuropathy, myelopathy, memory impairment, dementia, depression, and brain atrophy may occur in those with low B12 status [3]. According to one study, a neuropathy known as combined degeneration of the spinal cord, is one of the most debilitating manifestations of vitamin B12 deficiency [4]. Neurological and psychiatric symptoms have been seen in patients without related anemia or macrocytosis, with B12 concentrations in the previously defined range of low-normal. This highlights the need for the prevention of B12 deficiency [3]. The main dietary sources of B12 are animal products including meat, fish, eggs, and dairy products [3]. Other sources include B12-containing, fortified plant products such as cereals, plant-based milks, soy products, and B12-fortified yeast extract [5].

Populations at the highest risk for B12 deficiency include the elderly and those that follow a vegetarian or vegan diet. Deficiency within the elderly population is often the result of age-related gastric atrophy. This causes a decrease in acid and intrinsic factor production leading to B12 malabsorption [6]. It should be noted, however, that causes such as pernicious anemia and food-bound malabsorption account for less than half of poor B12 status among the elderly [3]. A high rate of deficiency among vegetarians or vegans exists because B12 is only naturally present in animal products, so those who do not consume diets high in fortified products are at risk [5].

The purpose of this review is to examine published case studies on vitamin B12 deficiency in adults. This will include an evaluation of B12 deficiency in regards to causes, biomarkers of B12 status, clinical manifestations, and treatment outcomes.

LITERATURE SEARCH

To identify published case studies on vitamin B12 deficiency in adults, the databases PubMed, ProQuest, ScienceDirect, and the Journal of Medical Case Reports were utilized. Searches with terms: vitamin B12 and deficiency was utilized for searches in ProQuest with “Adult” selected as the age group and “Case Study” selected as the document type. ScienceDirect searches included the terms: vitamin B12, deficiency, and case study using Journals as the content type. This was narrowed further by limiting the topics to just B12 deficiency and vitamin B12. The Journal of Medical Case Reports was searched using the terms vitamin B12, deficiency, and case study.

Searches with the terms: B12 in the title and case in the title were used for the literature searches within PubMed. Cross-referencing was employed within PubMed to identify related citations from initial search results. The total number of publications found in all databases was 353 manuscripts. After screening all publications, 89 were excluded because they were not case studies. An additional 62 were excluded as not being applicable to vitamin B12 deficiency. Seventy-eight were excluded due to not being available in English, 31 were excluded because children, adolescents, or pregnant women were described in the report, and four were excluded due to unavailability of full-text.

RESULTS

The literature search yielded a total of 89 applicable case studies, of which, 40 involved females and 49 involved males. Thirty-six cases included young adults in the age range of 18-40 years, 25 cases included those in middle adulthood aged 40-64 years, and 27 cases included elderly individuals aged 65+. One case did not report an age. Cases were reported from 28 countries in total.

The identified causes of B12 deficiency are varied, but can be grouped into four main categories. These categories are: (1) malnutrition (nutritional deficiency) (20 cases), (2) lack of intrinsic factor (IF) and/or malabsorption of protein-bound vitamin B12 (36 cases), (3) general malabsorption (8 cases), and (4) competition for vitamin B12 (nitrous oxide poisoning or metformin therapy) (11 cases) [7]. A total of 14 cases did not report a definitive cause of B12 deficiency.

Nutritional B12 Deficiency

Nutritional B12 deficiency has been attributed to cases of chronic alcoholism (1 case), and inadequate dietary intake (19 cases: 13 related to vegetarianism, 6 related to poor diet). One case of a 61 year old male with a history of excess alcohol consumption was reported [8]. Hematological values of B12 status were not reported [8].

Thirteen cases of vegetarianism related to B12 deficiency were reported [9-20]. These cases included seven males and six females aged 18-68 years. Six of these cases reported a serum B12 level between 31.6-150 pg/mL [9-14]. Five cases reported a serum B12 level of 65.1-125.4 pmol/L [15-18] and two cases reported serum B12 levels of 101 and 195 ng/L [19,20] Megaloblastic anemia was indicated in three cases, [9,16,19] normocytic anemia in one case [15] and a generally defined anemia referred to as B12 deficiency anemia was indicated in one case [10]. For the mean corpuscular volumes (MCV) reported values ranged from 84-144 fl [9,13,15-17,19]. Elevated homocysteine levels were demonstrated in three cases and were 28, 30.59, and 50 µmol/L respectively [13,18,20].

Six cases of malnutrition as a result of poor or insufficient diet were reported. These included three males and three females aged 21-73 years [21-26]. Serum B12 levels of 55, 79, and 140 pmol/L were reported in three cases [21-23]. Two cases reported serum B12 levels of 35 and <100 pg/mL [24,25]. One case indicated a serum B12 level of 54 ng/L[26]. MCV levels were reported in 3 cases and were 94.3, 108 and 125 fl respectively [21,23,26]. Homocysteine was reported as 88 µmol in one case [21] and serum holotranscobalamin was reported as 27.89 pmol/L in another three cases provided information on dietary habits likely leading to deficiency. One case of a 26 year old female indicated a very poor diet of corn snacks, chips, and fast food; and no consumption of vegetables for several years [26]. A case of a 21 year old male reported a very limited diet of toasted oats cereal without milk, bread, and french-fried potatoes. The patient had aversion to many food textures including meat [21]. A case of a 73 year old male reported infrequent intake of meat, but the patient did consume fish three to four times a week [23]. All other cases did not provide specific information on dietary habits [22,24,25].

Lack of Intrinsic Factor (IF)/Malabsorption of Protein-bound B12

Thirty-six cases reported B12 deficiency due to lack of IF or other causes of malabsorption of protein-bound B12. These included 22 males and 14 females ranging in age from 22 to 87 years [27-56].Their serum B12 levels ranged from 5-307 pg/mL [27-45], 51-338 ng/mL, [46-52] and 25-104 pmol/L [53-56]. Of MCV levels reported, values ranged from 80-122 fl [27,29,31,32,34] [36,39-41,43,44,46-54,56] Homocysteine levels were reported in nine cases total ranging in six cases from 23-150 µmol/L [34,42,44,47,54,55]. Three cases indicated homocysteine levels at 18 ng/mL, [40] >50 nmol/L, [33] and 120 mcg/L [50].

General malabsorption

Eight cases reported general malabsorption as related to B12 deficiency. These cases included six males and two females aged 18-73 years [57-64]. Serum B12 levels ranged from 60-169 pg/mL in five cases, [57-61] and were reported as 121 ng/mL, 349 ng/mL, and 1365 pmol/L in three cases [62-64]. Seven cases reported MCV levels which ranged from 81-108 fl [57-62,64]. Two cases indicated homocysteine levels of 64.4 µmol/L and 93 µmol/L [59,64]. Additionally, methymalonic acid (MMA) was reported as 722 nmol/L in one case [63].

Malabsorption occurred in three cases as a result of bowel resection due to midgut volvulus, [57] congenital necrotizing ileus, [59] and diffuse large B cell lymphoma (DLBCL) [60]. One individual experienced malabsorption due to issues at the terminal ileum [62]. One case indicated malabsorption of B12 due to an abnormal binding protein in the serum resulting in a high serum B12 level, but very low red blood cell B12 level [64]. Moreover, one case indicated functional B12 deficiency due to a failure of intracellular transport [63]. The other two cases only indicated a generalized malabsorption with no definitive cause stated, [58,61] one of these cases, however, did indicate Klebsialla pneumonia or malabsorption from the upper GI tract as a potential cause [61].

Competition for B12

Three cases were reviewed which presented post-operative occurrences of B12 deficiency as a result of nitrous oxide exposure during surgery. This included three males aged 52, 57, and 65 years [56,65,66]. Development of deficiency symptoms occurred at 7 days [65], 16 days [66], and 2 months [65] post-operative. Serum B12 status was reported as 135 pmol/L [65]

166 pmol/L, [65] and 30 µg/L [66].

Three studies presented cases of nitrous oxide induced vitamin B12 deficiency as a result of recreational misuse. These cases included two females and one male [67-69]. Specific age was not given in the first case but indicated that the patient was in their twenties, [67] the second case was of a 23 year old, [68] and the third was a 33 year old [69]. All patients inhaled nitrous oxide through whipped cream bulbs abusively (10-20 bulbs/day [67]; 130 bulbs/day[68], daily use for 4 weeks [69]). Serum B12 levels were 124 pmol/l, 125 pmol/l, and 202 pg/mL [67-69]. MCV levels were reported in two cases and were 92 and 95 fl respectively [67,69]. A Homocysteine level was reported in one case and was 48.4 µmol/L [69].

Metformin-induced vitamin B12 deficiency was reported in five cases. These cases included three females and two males aged 60-82 years [70-73]. Specific age was not reported in one case [72]. Serum B12 levels were 60 pg/mL, [70] 131 pg/mL, [71] 97 pmol/L, [72] and 125 pmol/L [72]. One case did not report the serum B12 level for the patient [73]. MCV levels were indicated in three cases and were 99.7, 104, and 120.3 fl respectively [71,72].

Unreported causes

A total of 14 cases did not report a definitive cause of B12 deficiency. These cases included six males and eight females aged 31-88 years [15,17,74-83]. Serum B12 levels were reported as ranging from 13.5-247 pg/mL [45,51,74-80] and 44-113 pmol/L [15,17,81,82]. One case indicated a serum B12 level of 60 ng/L [83]. MCV levels were reported in eight cases and ranged from 65.5-114.1 fl [15,51,74,76,78-80,83]. Homocysteine levels were indicated in three cases and were 12.3 µmol/L [51] and >50 µmol/L [45,81].

CLINICAL MANIFESTATIONS

Neurological impairments

A total of 43 cases involved patients with B12 deficiency-related neurological impairment. These patients ranged from 19-82 years of age and presented an array of symptoms (Table 1). A common clinical manifestation experienced by patient's studied with neurological impairment is paresthesia or tingling, numbness, and/or burning in the skin, which was indicated in 27 cases total [19,20,21,31-34,37,38,41,45-49,53,58,49-63,53,58,63-65,68,70,73,75,76]. Another prevalent clinical manifestation observed is ataxia or the lack of coordination of muscle movements, often accompanied by gait abnormalities. This was reported in 22 cases [13,18,21,31,37,38,41,45,46,49,50,51,55,62-67,78,79] Other symptoms commonly reported included weakness (13 cases) [19,21,34,37,42,45,46,62,64,65,68,72,75] and impaired cognitive abilities (9cases) [13,18,31,33,37,51,66,72,79]. Four cases indicated that Lhermitte's sign, an electrical sensation which moves down spine, was a prevalent symptom especially during neck flexion [32,45,64]. Three cases reported fatigue as a problematic occurrence [48,49,79].

Psychiatric abnormalities

A total of 16 cases involved patients with B12 deficiency-related psychiatric abnormalities. These patients ranged in age 23-78 years and exhibited a multitude of symptoms (Table 2). The most prevalent features of patients experiencing psychiatric abnormalities as a result of B12 deficiency included, delusions (5 cases) [39,40,60,61,69], irritability (5 cases), [14,40,43,59,77] and decreased interest (5 cases) [11,12,25,40,60]. Other manifestations included depression (4 cases) [12,25,39,60] and sleep disturbances (4 cases) [12,25,60,74] Symptoms such as confusion (3 cases), [39,40] fatigue (3 cases), [12,25,60] irrational behavior (3 cases) [22,69,77] and paranoia (3 cases) [40,59,74] were also observed. Hyperactivity, sexual indiscretion, social withdrawal, forgetfulness, and psychotic episodes were also seen in two cases each [43,77,11,74,22,14,59,40]. Lastly, a hallucination was a reported symptom in one case [82].

Oral manifestations

Thirteen cases reported oral manifestations of B12 deficiency, and included patients aged 19-88 years. These patients experienced varying symptoms outlined in (Table 3). The most prevalent symptoms were glossitis (4 cases), [56] recurrent aphthous stomatitis (4cases), [15,30] and pain and burning sensations in the mouth [16,23,52,83]. Additionally, increased sensitivity was another notable feature [23,52]. Other symptoms experienced included hoarseness and vocal fold palsy, [8] red stains on cheeks and tongue, [16] and epithelial dysplasia [83].

Dermatological manifestations

A total of five cases reported B12 deficiency-related dermatological manifestations. These included patients aged 25-54 years with symptoms outlined in (Table 4). Symptoms included hyperpigmentation (3 cases) [10,24,35] and skin lesions (2 cases) [17].

Rare manifestations

Ten cases presented symptoms that were not able to be categorized as neurological, psychiatric, oral, or dermatological and could be considered rare manifestations of B12 deficiency. One or more of these symptoms could potentially resign in the previously ascribed categories; however, the majority cannot be classified. The cases involved patients between the ages of 18 and 85 years, and exhibited the symptoms outlined in (Table 5) [9,26,29,44,54,57,81,80].

TREATMENT/OUTCOMES

The majority of cases reported B12 replacement therapy via intramuscular (IM) administration as the initiated treatment. A total of 59 cases utilized this method of B12 repletion, and staggered treatment approach was often utilized. This typically consisted of daily injections for a week or longer, followed by weekly injections, then monthly injections thereafter. Doses for IM B12 therapy ranged from 100 µg to 1000 µg. Nine cases indicated that B12 was administered parenterally, five at a dose of 1000 µg, [15,43,45] (3cases) one at 3000 µg, [13] and three unreported doses [38,75,76]. One case reported intravenous and IM B12 therapy [58]. Three cases indicated that oral B12 was given at 100 µg [52] and 1000 µg [10,82]. Fifteen cases did not report specific information regarding the method of B12 administration [26,32,39,42,50,53,59,66-68,72,73,78].

Treatment with B12 replacement therapy resulted in full recovery in 40 cases. Improvement in symptoms, but not full

Table 1: Characteristics of Patients with Neurologic Impairments.

Case/reference Number	Age	Sex	Symptoms	Serum B12 Status	Causes	Treatment
1 [33]	39 years	Male	• Distal upper extremity numbness • Fine motor difficulties	203 pg/mL	Lack of IF	(B12) Monthly injections
2 [19]	19 years	Male	• Painless weakness • Paresthesia • Numbness of palmar aspects of both hands	101 ng/L	Vegetarianism	(B12) IM therapy
3 [38]	56 years	Male	• Acute onset of paresthesia involving both hands • Difficulty walking • Inability to feel the ground	75 pg/mL	Lack of IF	Parenteral administration of vitamin B12
4 [58]	19 years	Male	• Gradually progressing tingling in both hands	<100 pg/mL	Malabsorption	(B12) Intravenous and IM injections
5 [20]	39 years	Male	• Progressive spastic paraparesis	195 ng/L	Vegetarianism	(B12) IM 1 mg/day for 1 week, weekly for 3 weeks, then every month
6 [13]	40 years	Male	• Acute onset of irrelevant speech and inability to comprehend • Involuntary movements of upper extremities • Unsteady gait	62.96 pg/mL	Vegetarianism	Parenteral (B12) 3000 µg/day for 1 month, then 1000 µg/month for 1 month
7 [18]	68 years	Male	• Acute onset of dizziness • Ataxia • Vomiting • Mildly impaired cognitive functions • Disorientation in time • Short-term memory loss	121 pmol/L	Vegetarianism	IM (B12) 1000 µg/day for 1 week, 1/week for 4 weeks, then oral administration
8 [21]	21 years	Male	• Progressive gait instability • Weakness in legs • Paresthesia in feet • Difficulty concentrating	55 pmol/L	Malnutrition (poor diet)	IM (B12) for 1 week, weekly injections for 1 month, then monthly injections
9 [46]	35 years	Female	• Progressive unsteadiness of gait • Tendency to fall toward the left • Numbness in both legs	100 ng/mL	Lack of IF	IM (B12) 1000 µg
10 [31]	35 years	Male	• Progressive unsteadiness • Slurring of speech • Alteration in mood • Numbness in both legs	<44 pg/mL	Lack of IF	IM (B12) 1 mg daily for 1 week, then monthly injections
11 [47]	37 years	Female	• Burning pain in lower limbs	51 ng/L	Lack of IF	IM (B12) 5000 µg/week for 1 month than 1000 µg/week
12 [47]	61 years	Female	• Pain • Cramps • Distal parethesias in lower legs	53 ng/L	Lack of IF	IM (B12) 1000 µg/day
13 [32]	38 years	Female	• Fatigue • Electric dysesthesia with neck flexion (Lhermitte's sign)	<50 pg/mL	Lack of IF	(B12) 500 µg biweekly
14 [32]	44 years	Male	• Fatigue • Numbness in extremities • Intermittent electric dysesthesia associated with neck flexion (Lhermitte's sign)	42 pg/mL	Lack of IF	B12 therapy
15 [34]	42 years	Female	• Numbness and tingling feet • Symmetrical weakness of lower extremities • Urinary incontinence • Sensory loss of perineal region	<150 pg/mL	Lack of IF	IM (B12) 1000 µg/day for 7 days, weekly for 3 weeks, then monthly
16 [48]	44 years	Male	• Shortness of breath • Fatigue • Paresthesia	70 ng/L	Lack of IF	IM (B12) 1000 µg/day for 1 week, then weekly for 1 month, then monthly
17 [53]	44 years	Male	• Constant tolerable pains in the lumbar area • Numbness in the lower limbs	75 pmol/L	Lack of IF	(B12) 1000 g for 30 days, then 500 g for 15 days
18 [36]	55 years	Male	• Bradykinesia • Tremors of hands	5 pg/mL	Lack of IF	IM (B12) 1000 mg/day for 3 days then 1/week for 4 weeks
19 [37]	55 years	Male	• Weakness and numbness in extremities • Difficulty walking • Deterioration of mental activities	<30 pg/mL	Lack of IF	IM (B12) 1000 µg/day for 7 days, then 1000 µg/week

Case/reference Number	Age	Sex	Symptoms	Serum B12 Status	Causes	Treatment
20 [49]	57 years	Male	• Difficulty in walking • Easily fatigued • Broad-based gait • Numbness and tingling and hands and feet • Loss of positional sense • Dysesthesia below the knees	146 ng/L	Lack of IF	IM (B12) 1000 µg/day for 3 weeks, monthly for 6 months, then 100 µg oral/daily
21 [55]	62 years	Male	• Choreatic movements in upper arms and head	104 pmol/L	Lack of IF	IM (B12) 1mg/day for 10 days, then weekly
22 [50]	66 years	Female	• Ataxia of stance and gait	338 ng/L	Lack of IF	(B12) 1 mg/day for 12 days, then 1/week
23 [51]	70 years	Female	• History of imbalance • Gait disturbance • Memory problems	247 pg/mL	Uknown	IM (B12) 1mg/day for 5 days, then monthly
24 [51]	74 years	Female	• Gait disturbance • Imbalance • Blurred vision	86 ng/mL	Lack of IF	IM (B12) 1 mg/day for 10 days, then monthly
25 [41]	77 years	Male	• Unstable gait • Urinary urgency • Clumsiness of hands • Tingling sensations in legs • Occasional dizziness	38 pg/mL	Lack of IF	IM (B12) 1mg/day for 1 week then 1 mg/month
26 [42]	78 years	Male	• Weakness in the left arm and shoulder • Discomfort and difficulty in dressing	116 pg/mL	Lack of IF	Not reported
27 [45]	55 years	Male	• Paresthesias • Mild weakness in both hands and feet • Electric shock sensations • Jerking movements of abdominal muscles	142 pg/mL	Unknown	Parenteral (B12) 1000 µg/month
28 [45]	87 years	Male	• Progressively weakening gait • Abdominal jerks	<100 pg/mL	Lack of IF	IM (B12) 1000 µg/month
29 [64]	28 years	Male	• Lethargy • Anxiety • Depression • Paresthesia of hands and feet • Weakness of legs • Ataxia of gait • Lhermitte's symptom	1365 pmol/L	Malabsorption	IM (B12) 1 mg weekly
30 [62]	35 years	Male	• Progressive weakness of lower limbs • Unsteadiness of gait • Weakness of grip • Urgency and precipitancy of urine	121 ng/L	Malabsorption	IM (B12) 1000 µg/day for 2 weeks, weekly for 2 months, then monthly
31 [63]	73 years	Female	• Progressive gait deterioration • Urinary urgency • Spastic paraparesis with marked distal proprioceptive loss	349 ng/L	Malabsorption	IM (B12) 3 monthly injections
32 [65]	57 years	Male	• Clumsiness • Weakness of both hands • Tingling of fingers, arms and chest • Unsteadiness • Gait imbalance • Paresthesia	135 pmol/L	Nitrous oxide exposure	IM (B12) 1000 µg/day for five days
33 [65]	52 years	Male	• Paresthesia of feet, trunk, chest, and arms • Weakness and clumsiness of all limbs	166 pmol/L	Nitrous oxide exposure	IM (B12) 5000 µg/day for five days
34 [66]	65 years	Male	• Problems walking • Memory loss	<30 µg/L	Nitrous oxide exposure	Replacement B12 therapy
35 [67]	20's	Female	• Increasing difficulty in mobilizing	124 pmol/L	Nitrous oxide exposure	B12 replacement therapy
36 [68]	23 years	Female	• Profound tetraparesis • Progressive limb weakness	125 pmol/L	Nitrous oxide exposure	(B12) 5000 µg/day for 12 days
37 [70]	60 years	Male	• Behavior changes • Tingling numbness of both hands and feet	60 pg/mL	Metformin therapy	IM (B12) once a week for 4 weeks
38 [72]	82 years	Female	• Memory loss • Progressive leg weakness	97 pmol/L	Metformin therapy	(B12) 1000 µg on alternate days for 5 days followed by 1000 µg monthly
39 [73]	69 years	Male	• Numbness in feet	Not reported	Metformin therapy	IM B12 therapy

Case/reference Number	Age	Sex	Symptoms	Serum B12 Status	Causes	Treatment
40 [75]	35 years	Female	• Progressive weakness in lower limbs • Tingling and paresthesia • Numbness in feet and hands	13.5 pg/mL	Unknown	Parenteral B12 therapy for 6 months
41 [76]	38 years	Female	• Progressive hand numbness and tingling • Numbness of feet	72 pg/mL	Unknown	Parenteral B12 therapy
42 [79]	76 years	Female	• Forgetfulness • Reading difficulty • Headaches • Fatigue • Weight loss • Visual impairment • Gait abnormalities	78 pg/mL	Unknown	IM (B12) 1000 µg monthly
43 [78]	71 years	Male	• Progressive right hemichorea	124 pg/mL	Unknown	(B12) 5000 µg daily for 4 weeks, 2x/week for one month, then monthly

Table 2: Characteristics of Patients with Psychiatric Abnormalities.

Case/reference Number	Age	Sex	Symptoms	Serum B12 Status	Causes	Treatment
1 [61]	65 years	Male	• Persecutory delusions	110 pg/mL	Malabsorption	(B12) Daily intramuscular at 1000 µg/d
2 [39]	64 years	Male	• Confusion • Collapse • Deterioration of work efficiency	307 pg/mL	Lack of IF	Substitution of vitamin B12
3 [39]	77 years	Male	• Delusional fear of impoverishment • Disoriented • Depressed mood	203 pg/mL	Lack of IF	Vitamin B12
4 [43]	81 years	Male	• Irritable mood • Hyperactivity • Decreased need for sleep • Gradiosity • Sexual indiscretion • Reckless and agitated behavior	116 pg/mL	Lack of IF	(B12) 1000 µg i.v., for 1 week, then with weekly injections at the same dose.
5 [11]	27 years	Male	• Forgetfulness • Social withdrawal • Paucity of speech • Decreased interest • Apathy	<50 pg/mL	Vegetarianism	IM (B12) injections
6 [12]	33 years	Female	• Sad mood • Fatigue • Lack of interest • Sleep disturbances • Weight loss	82 pg/mL	Vegetarianism	IM (B12) 1000 ng/day for 10 days
7 [14]	52 years	Female	• Catatonia • Mute • Odd motor movements • Wavy flexibility • Active negativism • Perplexed look • Incontinence	150 pg/mL	Vegetarianism	IM (B12) 1000 µg on alternating days for 3 days plus an oral tablet daily. Followed by weekly IM (B12)
8 [25]	66 years	Female	• Sad mood • Lack of energy, interest, and motivation • Sleep disturbances	<100 pg/mL	Malnutrition	Series of IM (B12) injections
9 [22]	67 years	Female	• Irrational behavior • Tremor in hand • Deteriorating handwriting • Forgetfulness	79 pmol/L	Malnutrition	IM (B12) 1000 µg/day
10 [40]	72 years	Male	• Apathy • Irritability • Deterioration of attention and memory • Psychotic episodes • Paranoid thoughts • Jealous delusions	54 pg/mL	Lack of IF	IM (B12) 1000 µg 3x/week for 45 days, weekly for 45 days, then monthly
11 [59]	23 years	Female	• Distress • Catatonic • Mute • Paranoid	<100 pg/mL	Malabsorption	Aggressive B12 supplementation

Case/reference Number	Age	Sex	Symptoms	Serum B12 Status	Causes	Treatment
12 [60]	64 years	Male	• Depressed mood • Anhedonia and loss of interest • Loss of appetite and weight loss • Difficulty with falling asleep and concentrating • Fatigue • Delusions	169 pg/mL	Malabsorption	IM (B12) 1000 µg/day for 2 weeks then weekly for 2 weeks, then continuous treatment
13 [69]	33 years	Female	• Bizarre behavior • Delusions	202 pg/mL	Nitrous oxide exposure	IM (B12) 1000 µg every day for one week, then every month for one month
14 [74]	31 years	Male	• Insomnia • Suspiciousness • Hearing voices • Social withdrawal • Functional impairment	201 pg/mL	Unknown	IM (B12) daily for 1 week, then once a week for 4 weeks
15 [77]	35 years	Female	• Manic symptoms • Gradiosity • Hyperactivity • Sexual indiscretion • Hyperphagia • Irritable mood • Reckless behavior • Flight of ideas • Overbearing manner	60 pg/mL	Unknown	IM (B12) 1000 µg/day for a week, weekly for one month, then monthly
16 [82]	78 years	Female	• Visual hallucinations	44 pmol/L	Unknown	Oral vitamin (B12) 1mg daily

Table 3: Characteristics of Patients with Oral Manifestations.

Case/reference Number	Age	Sex	Symptoms	Serum B12 Status	Causes	Treatment
1 [23]	73 years	Male	• Pain and burning sensation in tongue • Increased sensitivity to tongue's sensations (post chemical exposure)	140 pmol/L	Malnutrition	(B12) Individual injectable IM administration
2 [56]	54 years	Female	• Stomatitis • Glossitis	<44 pmol/L	Unknown	(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly
3[56]	36 years	Male	• Migratory glossitis	<44 pmol/L	Unknown	(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly
4 [56]	33 years	Female	• Acute glossitis	<44 pmol/L	Unknown	(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly
5 [56]	68 years	Female	• Glossitis	25 pmol/L	Unknown	(B12) 1 mg/day IM for 5 days, followed by 1 mg monthly
6 [8]	61 years	Male	• Gradually progressive hoarsness • Vocal fold palsy	Not reported	Excessive alcohol consumption	(B12) IM administration
7 [16]	41 years	Female	• Difficulty in eating foods (banana/ tomato) because of burning sensation • Presence of red stains on inside of cheeks and tongue	Not reported	Vegetarianism	Monthly injections of vitamin B12 replacement therapy
8 [15]	30 years	Female	• Recurrent aphthous stomatitis (canker sores)	65.1 pmol/L	Semi-vegetarianism	(B12) 1000 µg parenteral 2x/week for 6 weeks followed by injections 1x/month for 1 year
9[15]	28 years	Male	• Recurrent aphthous stomatitis (canker sores)	124.5 pmol/L	Semi-vegetarianism	(B12) 1000 µg parenteral 2x/week for 6 weeks followed by injections 1x/month for 1 year
10[15]	19 years	Female	• Recurrent aphthous stomatitis (canker sores)	64.2 pmol/L	Unknown	(B12) 1000 µg parenteral 2x/week for 6 weeks followed by injections 1x/month for 1 year
11[30]	31 years	Female	• Recurrent aphthous stomatitis (canker sores)	< 50 pg/mL	Lack of IF	IM (B12) 1000 µg/day for 1 week, followed by once every two weeks
12 [52]	73 years	Female	• Sore, burning tongue • Increased tongue sensitivity	144 ng/L	Lack of IF	Oral B12 100 µg/day
13 [83]	88 years	Female	• Tongue and mouth discomfort • Oral epithelial dysplasia	60 ng/L	Unknown	IM (B12) 1 mg every 3 days

Table 4: Characteristics of Patients with Dermatological Manifestations.

Case/reference Number	Age	Sex	Symptoms	Serum B12 Status	Causes	Treatment
1 [10]	25 years	Female	• Blackish discoloration of the skin on knuckles	31.6 pg/mL	Vegetarianism	Oral B12 replacement
2 [17]	34 years	Female	• Skin lesions on feet	113 pmol/L	Unknown	IM (B12) 1000 µg/day
3[17]	54 years	Female	• Skin lesions on neck and upper and lower limbs	100 pmol/L	Vegetarianism	IM (B12) 1000 µg/day
4 [24]	54 years	Male	• Darkening of hands, feet, and tongue (hyperpigmentation)	35 pg/mL	Malnutrition	IM (B12) 1 mg every week for 2 months, then every month for 3 months
5 [35]	43 years	Male	• Increased skin pigmentation	34.34 pg/mL	Lack of IF	IM (B12) 100 mg/day for 7 days, then 2x/week for 3 weeks, then 100 mg once a month

Table 5: Characteristics of Patients with Rare Manifestations.

Case/reference Number	Age	Sex	Symptoms	Serum B12 Status	Causes	Treatment
1[9]	18 years	Male	• Fatigue • High-grade pyrexia (fever)	105 pg/mL	Vegetarianism	(B12) 1000 mcg/day IM
2 [26]	26 years	Female	• Gradual and painless visual loss	54 ng/L	Malnutrition (poor diet)	B12 supplementation
3 [27]	22 years	Female	• Malaise • Anorexia • Exercise intolerance	52 pg/mL	Lack of IF	IM (B12) 100 µg/day for 10 days, followed by monthly injections
4 [28]	24 years	Male	• Persistent watery diarrhea • Anorexia • Weight loss	110 pg/mL	Lack of IF	IM (B12) monthly
5 [29]	26 years	Male	• Complex partial seizures • Social withdrawal • Memory impairment	26 pg/mL	Lack of IF	IM (B12) injections
6 [54]	52 years	Male	• Shortness of breath • General weakness • Weight loss • Sore tongue • Pancytopenia	52 pmol/L	Lack of IF	IM (B12) for 7 days, then weekly for 4 weeks, then once a month
7 [44]	85 years	Female	• Intermittent, brief, painless involuntary movements in the abdominal muscles	<90 pg/mL	Lack of IF	IM (B12) 1000 µg/day for 7 days, then 1000 µg/ week
8 [57]	18 years	Male	• Short stature • Prepubertal sexual maturation • Exertional dyspnea	60 pg/mL	Malabsorption	IM (B12) 100 µg/day for 14 days, then 50 µg every other week
9 [81]	59 years	Male	• Collapse to unconsciousness • Generalized tonic-clonic seizure activity • Mild headaches • Occasional diaphoresis	90 pmol/L	Unknown	IM (B12) replacement therapy
10 [80]	80 years	Male	• Extreme fatigue • Fainting • Jaundice • Headache • Vertigo • Insomnia • Nocturnal dyspnea	129 pg/mL	Unknown	IM (B12) 1 mg/day for 25 days, 1 mg/week for 8 weeks, then monthly

remission was observed in 39 cases. Five cases indicated little to no improvement in symptoms, [42,51,53,63,73] and three cases did not report a treatment outcome [27,30,43].

BIOMARKERS OF B12 STATUS

Biomarkers of B12 status reported in the cases included serum B12 levels, mean corpuscular volume (MCV), and serum homocysteine. Serum methylmalonic acid (MMA) is an additional biomarker of B12 status; however, it was not widely reported in the cases reviewed. Serum B12 level was reported in all but two cases [8,16]. MCV levels were reported in 53 cases and serum homocysteine levels in 13 cases.

A notable case to report was of a 40 years of age male patient who initially had normal B12 level, however, he demonstrated progressive neurological symptoms and repeat MR imaging indicated posterior cervical cord lesions. A second test of B12 levels indicated a low B12 status of 41 pg/mL. The authors recommend that in cases where B12 is in the low normal range at first test, levels of methylmalonic acid and homocysteine should

be checked to confirm a diagnosis [33].

DISCUSSION

B12 deficiency can occur due to a number of causes and can affect people of various ages and backgrounds. As formerly noted, the causes of B12 deficiency can be grouped into four main categories including, nutritional B12 deficiency, lack of IF or malabsorption of protein-bound B12, general malabsorption, and competition for B12.

As already mentioned, B12 is naturally present only in meats and foods of animal origin. Therefore, individuals that do not eat any animal products, such as vegans, are at high risk for deficiency if they do not consume adequate amounts of fortified products or supplements. A total of 13 cases reported deficiency due to vegetarianis [9-20]. Of these, six were vegetarian (1 lacto-vegetarian), [11,12,14,17-19] five were vegan, [9,10,13,16,20] and two were semi-vegetarian [15]. Three cases reported diet durations for the patients. These cases included one life-long vegan, [9] one life-long vegetarian, [11] and one vegan who had followed the diet for 2.5 years [16]. Previous studies have shown that compared to omnivores and vegetarians, vegans have a lower average serum concentration of B12 [4]. Some studies have also suggested that compared to omnivores, vegetarians have lower B12 serum concentrations [4]. One review indicated that vegetarians develop deficiency regardless of the type of diet, geographical location where they reside, or any other factors [84]. As such, it is imperative that those who follow a vegetarian or vegan diet consume adequate amounts of B12 fortified food products and/or take supplements containing B12 to prevent deficiency.

Lack of IF is the most common cause of impaired vitamin B12 absorption, which can be seen in patients who suffer from gastric atrophy [17]. Malabsorption of protein-bound vitamin B12 is often observed in the elderly population where gastric acid is not produced in sufficient amounts to proteolyze B12 from proteins [17]. This is often the result of atrophic gastritis where the fundus glands and parietal cell mass are reduced [17]. A total of 36 cases reported B12 deficiency due to lack of IF or malabsorption of protein-bound B12. This represented the most common cause of deficiency among the cases reviewed. Although lack of IF, as mentioned is commonly observed in the elderly population, it is not exclusive to this population. Of the cases reviewed, the majority (22 cases) represented patients below the age of 65. Moreover, it appears that lack of IF could be a prominent cause of B12 deficiency among young and middle-aged adults. The Dietary Guidelines for Americans currently recommends that individuals aged 50 years and older should take a B12 supplement [85]. The findings of the cases reviewed indicate that this recommendation may have to be extended to individuals in younger age groups.

General malabsorption leading to B12 deficiency can be encountered among individuals having undergone bowel resection especially at the terminal ileum. This is because the terminal ileum is the site of B12 absorption [2]. Three cases presented B12 deficiency due to bowel resection. One case involved small bowel resection, [57] one involved resection due to congenital necrotizing ileus, [59] and one had a resection of the terminal ileum due to DLBCL [60]. Individuals having undergone bowel resection should be screened for B12 deficiency at regular intervals. Moreover, a prudent measure would be for these patients to receive regular B12 injections, as the use of supplements may not be effective in correcting deficiency due to their malabsorptive state.

Competition for vitamin B12 leading to deficiency can occur with use of some medications [17]. One of these medications is nitrous oxide. Nitrous oxide irreversibly oxidizes the cobalt ion of B12 and therefore inactivates it [68]. Nitrous oxide, or "laughing gas" is often used as an analgesic before short medical procedures to elevate mood.[68] Three cases were reviewed which presented post-operative occurrences of B12 deficiency as a result of nitrous oxide exposure during surgery [65,66]. Nitrous oxide is also misused recreationally by inhalation of the gas from whipped cream dispensers. Three reports presented cases of nitrous oxide induced vitamin B12 deficiency as a result of recreational misuse [67-69]. B12 deficiency resulting from nitrous oxide exposure is well documented and can result in subacute combined degeneration (SCD) of the spinal cord [65]. SCD of the spinal cord involves degeneration of the posterior and lateral columns [67]. Of the cases involving B12 deficiency due to nitrous oxide exposure, five reported SCD as a resulting complication [65-69]. Individuals having undergone surgery where nitrous oxide was used as an analgesic should be made aware of the potential effect this has on B12 status. Additionally, they should be screened post-operatively for indicators of B12 deficiency. Physicians should also be made aware of the detrimental effects associated with the recreational misuse of nitrous oxide in regards to B12 deficiency, so they will be able to treat patients quickly and appropriately.

Metformin for the treatment of diabetes is another medication that when used can lead to B12 deficiency. Although the responsible mechanism for metformin inducing B12 deficiency is controversial it is proposed that metformin affects the calcium-dependent ileal cell membrane receptors needed for B12-intrinsic factor uptake [72]. Metformin-induced vitamin B12 deficiency was indicated in five cases [70-73]. Metformin is the leading antidiabetic drug sold in the US with more than 30 million generic prescriptions distributed to patients in 2009 [86]. Approximately 30% of patients undergoing metformin therapy experience B12 malabsorption [86]. It is indicated that metformin reduces the absorption of B12 by up to 30% and reduces serum B12 concentrations by 5-10% [86]. Moreover, B12 deficiency may exacerbate many diabetes co-morbidities such as poor circulation and neuropathy. Thus it is imperative that screening for B12 deficiency occurs among patients undergoing metformin therapy.

The clinical manifestations of B12 deficiency are varied and include neurological, psychiatric, oral, and dermatological signs and symptoms. A total of 43 cases involved neurological complications as a result of B12 deficiency. The main features of neurological impairment observed in the cases reviewed included paresthesia (27 cases), ataxia (22 cases), and weakness (13 cases) of the extremities. Psychiatric abnormalities were observed in 16 cases. The main features of psychiatric manifestations observed included delusions (5 cases), irritability (5 cases), decreased interest (5 cases), and sleep disturbances (4 cases). Oral manifestations were reported in 13 cases, and included symptoms

such as glossitis (4 cases), recurrent aphthous stomatitis (4 cases), and pain and burning sensations in the mouth (4 cases). Dermatological symptoms were indicated in five cases and the most prevalent manifestation was hyperpigmentation (3 cases).

Clinical manifestations of B12 deficiency were observed in nine cases where serum B12 levels were higher than what is commonly accepted as a deficiency [33,39,50,51,63,64,69,74]. Six of these cases reported serum B12 levels from 201-307 pg/mL, [33,39,51,69,74] two indicated levels of 338 and 349 ng/mL, [50,63] and one case reported a very high serum B12 level of 1365 pmol/L [64]. Further investigation of this patient with functional B12 deficiency indicated that although serum B12 levels were high, the patient had a very low red blood cell vitamin B12 level and high levels of homocysteine and MMA. The findings of these cases confirm that serum B12 levels may not be the most reliable method for assessment of B12 status and that other biomarkers of B12 status should be utilized in concurrence with serum B12 levels to make an accurate diagnosis. Studies have indicated that serum or plasma B12 and MCV can be unreliable methods for the assessment of B12 levels [87]. Transcobalamin II (TCII) and MMA are currently considered the most precise assessment methods [87].

There are various methods of B12 replacement therapy included parenteral (or intravenous) replacement, intramuscular (IM) therapy, or oral B12 replacement. The vast majority of cases (59 cases) reviewed used the IM method to restore serum B12 levels, with many cases utilizing a dose of 1000 μg in a staggered therapeutic approach. Forty cases reported complete remission of deficiency symptoms with B12 therapy, while 39 cases reported improvement. This highlights the need for emphasis on the prevention of B12 deficiency as many of the symptoms, especially neurological, did not reverse completely with B12 replacement therapy. All but one patient [52] experiencing oral manifestations of B12 deficiency experienced complete resolution of symptoms (one case was unreported) [30]. Similarly, all but one case experiencing dermatological symptoms indicated full recovery [17]. This indicates that B12 deficiency manifesting as oral or dermatological symptoms may be relatively easy to treat. Moreover, the five cases which reported little to no improvement in symptoms were all neurological, and may indicate that these symptoms are resistant to treatment and in some instances may not be reversible [42,51,53,63,73]. In these cases, prevention may be the best medicine.

B12 deficiency can be prevented by adequate intake of B12 containing food products such as meat, fish, eggs, and dairy products; [3] or B12 containing fortified plant products such as cereals, plant-based milks, soy products, and B12-fortified yeast extract. However, meat and animal products are often recommended to be limited due to either prevention or management of chronic health conditions, while fortified foods usually contain small doses of this vitamin. If dietary adequacy is a probable cause, B12 containing supplements should be considered. Another method to prevent deficiency that has been proposed is the fortification of flour with B12 [87]. In order to be effective among groups at a high risk for deficiency the flour would likely have to be fortified at a dose of 100 μg or greater per 100 g [87]. Keller et al. suggested a novel way of preventing B12 deficiency using B12-fortified tooth paste [88]. In their study with vegans and vegetarians with low B12 status all biomarkers measured including TCII, total homocysteine and serum B12 values were normalized after 5 weeks duration of the experiment. Unfortunately, they did not report the dose of fortification of the toothpaste.

Biomarkers of B12 status include serum B12 level, MCV, serum homocysteine, and MMA. Serum B12 levels were overwhelmingly utilized as the indicator of B12 status having been utilized in all but two cases. MCV levels were reported in 53 cases and homocysteine in 13 cases. To achieve more reliable B12 status, clinicians should consider utilizing two different assessment methods, especially MMA and TCII.

REFERENCES

1. Brody T. Nutritional Biochemistry. 2nd Edition. San Diego CA: Academic Press; 1999.
2. Headstrom PD, Rulyak SJ, Lee SD. Prevalence of and risk factors for vitamin B(12) deficiency in patients with Crohn's disease. Inflamm Bowel Dis. 2008; 14: 217-223.
3. Vogiatzoglou A, Smith AD, Nurk E, Berstad P, Drevon CA, Ueland PM, et al. Dietary sources of vitamin B-12 and their association with plasma vitamin B-12 concentrations in the general population: the Hordaland Homocysteine Study. Am J Clin Nutr. 2009; 89: 1078-1087.
4. Selhub J, Morris MS, Jacques PF, Rosenberg IH. Folate-vitamin B-12 interaction in relation to cognitive impairment, anemia, and biochemical indicators of vitamin B-12 deficiency. Am J Clin Nutr. 2009; 89: 702S-6S.
5. Gilsing AM, Crowe FL, Lloyd-Wright Z, Sanders TA, Appleby PN, Allen NE, et al. Serum concentrations of vitamin B12 and folate in British male omnivores, vegetarians and vegans: results from a cross-sectional analysis of the EPIC-Oxford cohort study. Eur J Clin Nutr. 2010; 64: 933-939.
6. Dangour AD, Allen E, Clarke R, Elbourne D, Fasey N, Fletcher AE, et al. A randomised controlled trial investigating the effect of vitamin B12 supplementation on neurological function in healthy older people: the Older People and Enhanced Neurological function (OPEN) study protocol [ISRCTN54195799]. Nutr J. 2011.
7. Goebels N, Soyka M. Dementia associated with vitamin B(12) deficiency: presentation of two cases and review of the literature. J Neuropsychiatry Clin Neurosci. 2000; 12: 389-394.
8. Green R, Kara N, Cocks H. Vitamin B, deficiency: an unusual cause of vocal fold palsy. J Laryngol Otol. 2011; 125: 1309-1311.
9. Negi RC, Kumar J, Kumar V, Singh K, Bharti V, Gupta D, et al. Vitamin B12 deficiency presenting as pyrexia. J Assoc Physicians India. 2011; 59: 379-380.
10. Kumar V, Sharma V. Medical image. Reversible knuckle hyperpigmentation in B12 deficiency. N Z Med J. 2011; 124: 98-99.
11. Sahoo MK, Avasthi A, Singh P. Negative symptoms presenting as neuropsychiatric manifestation of vitamin B12 deficiency. Indian J Psychiatry. 2011; 53: 370-371.
12. Milanlioglu A. Vitamin B12 deficiency and depression. Journal of Clinical and Experimental Investigations. 2011; 2: 455-456.
13. Shyambabu C, Sinha S, Taly AB, Vijayan J, Kovoor JM. Serum vitamin B12 deficiency and hyperhomocystinemia: a reversible cause of acute chorea, cerebellar ataxia in an adult with cerebral ischemia. J Neurol Sci. 2008; 273: 152-154.

14. Berry N, Sagar R, Tripathi BM. Catatonia and other psychiatric symptoms with vitamin B12 deficiency. Acta Psychiatr Scand. 2003; 108: 156-159.

15. Volkov I, Rudoy I, Abu-Rabia U, Masalha T, Masalha R. Case report: Recurrent aphthous stomatitis responds to vitamin B12 treatment. Can Fam Physician. 2005; 51: 844-845.

16. Pontes HA, Neto NC, Ferreira KB, Fonseca FP, Vallinoto GM, Pontes FS, et al. Oral manifestations of vitamin B12 deficiency: a case report. J Can Dent Assoc. 2009; 75: 533-537.

17. Kannan R, Ng MJ. Cutaneous lesions and vitamin B12 deficiency: an often-forgotten link. Can Fam Physician. 2008; 54: 529-532.

18. Singh B, Arora S. Acute presentation of dizziness in vitamin B12 deficient old patient of cardiac disease: a case report. Clin Chim Acta. 2010; 411: 2104-2106.

19. Ng VW, Gross M, Clifton A. Case report: MR appearances in vitamin B12 neuropathy. Clin Radiol. 1997; 52: 394-396.

20. Cheng SH, Chang MH, Soong BW, Chen CW, Lee YC. Spastic paraparesis as a manifestation of metabolic vitamin B12 deficiency: a case report. J Neurol. 2005; 252: 1125-1126.

21. Wong CL, Van Spall HG, Hassan KA, Coret-Simon J, Sahlas DJ, Shumak SL. A young man with deep vein thrombosis, hyperhomocysteinemia and cobalamin deficiency. CMAJ. 2008; 178: 279-281.

22. Slade TB, Bharadwaj RS. A case of acute behavioral disturbance associated with vitamin b(12) deficiency. Prim Care Companion J Clin Psychiatry. 2010; 12.

23. De Giuseppe R, Novembrino C, Guzzi G, Pigatto PD, Bamonti F. Burning mouth syndrome and vitamin B12 deficiency. J Eur Acad Dermatol Venereol. 2011; 25: 869-870.

24. Hoffman CF, Palmer DM, Papadopoulos D. Vitamin B12 deficiency: a case report of ongoing cutaneous hyperpigmentation. Cutis. 2003; 71: 127-130.

25. Hanna S, Lachover L, Rajarethinam RP. Vitamin b, deficiency and depression in the elderly: review and case report. Prim Care Companion J Clin Psychiatry. 2009; 11: 269-270.

26. Taubert M, Dowd TC, Wood A. Malnutrition and bilateral central retinal vein occlusion in a young woman: a case report. J Med Case Rep. 2008; 2: 77.

27. Chen SH, Hung CS, Yang CP, Lo FS, Hsu HH. Coexistence of megaloblastic anemia and iron deficiency anemia in a young woman with chronic lymphocytic thyroiditis. Int J Hematol. 2006; 84: 238-241.

28. Quigley EM, Carmichael HA, Watkinson G. Adult celiac disease (celiac sprue), pernicious anemia and IgA deficiency. Case report and review of the relationships between vitamin B12 deficiency, small intestinal mucosal disease and immunoglobulin deficiency. J Clin Gastroenterol. 1986; 8: 277-281.

29. Kumar S. Recurrent seizures: an unusual manifestation of vitamin B12 deficiency. Neurol India. 2004; 52: 122-123.

30. Palopoli J, Waxman J. Recurrent aphthous stomatitis and vitamin B12 deficiency. South Med J. 1990; 83: 475-477.

31. Molloy A, Cawley N, Ali E, Connolly S, Tubridy N, Hutchinson M. A pernicious leucoencephalopathy. Ir Med J. 2009; 102: 292-294.

32. Butler WM, Taylor HG, Diehl LF. Lhermitte's sign in cobalamin (vitamin B12) deficiency. JAMA. 1981; 245: 1059.

33. Makdsi F, Kadrie T. Sub-acute combined degeneration with an initially normal level of vitamin B12: a case report. Cases J. 2009; 2: 6944.

34. Puntambekar P, Basha MM, Zak IT, Madhavan R. Rare sensory and autonomic disturbances associated with vitamin B12 deficiency. J Neurol Sci. 2009; 287: 285-287.

35. Noppakun N, Swasdikul D. Reversible hyperpigmentation of skin and nails with white hair due to vitamin B12 deficiency. Arch Dermatol. 1986; 122: 896-899.

36. Kumar S. Vitamin B12 deficiency presenting with an acute reversible extrapyramidal syndrome. Neurol India. 2004; 52: 507-509.

37. Celik M, Barkut IK, Oncel C, Forta H. Involuntary movements associated with vitamin B12 deficiency. Parkinsonism Relat Disord. 2003; 10: 55-57.

38. Srikanth SG, Jayakumar PN, Vasudev MK, Taly AB, Chandrashekar HS. MRI in subacute combined degeneration of spinal cord: a case report and review of literature. Neurol India. 2002; 50: 310-312.

39. Goebels N, Soyka M. Dementia associated with vitamin B(12) deficiency: presentation of two cases and review of the literature. J Neuropsychiatry Clin Neurosci. 2000; 12: 389-394.

40. Blundo C, Marin D, Ricci M. Vitamin B12 deficiency associated with symptoms of frontotemporal dementia. Neurol Sci. 2011; 32: 101-105.

41. Toru S, Yokota T, Inaba A, Yamawaki M, Yamada M, Mizusawa H, et al. Autonomic dysfunction and orthostatic hypotention caused by vitamin B12 deficiency. J Neurol Neurosurg Psychiatry. 1999; 66: 804-805.

42. Rison RA, Beydoun SR. Amyotrophic lateral sclerosis-motor neuron disease, monoclonal gammopathy, hyperparathyroidism, and B12 deficiency: case report and review of the literature. J Med Case Rep. 2010; 4: 298.

43. Goggans FC. A case of mania secondary to vitamin B12 deficiency. Am J Psychiatry. 1984; 141: 300-301.

44. Dogan EA, Yuruten B. Spinal myoclonus associated with vitamin B12 deficiency. Clin Neurol Neurosurg. 2007; 109: 827-829.

45. Tsao JW, Cooper EC. Reflex-sensitive spinal segmental myoclonus associated with vitamin B12 deficiency. Neurology. 2003; 61: 867-868.

46. Perold JG. Vitamin B12 neuropathy in the absence of anaemia. A case report. S Afr Med J. 1981; 59: 570.

47. Dalla Torre C, Lucchetta M, Cacciavillani M, Campagnolo M, Manara R, Briani C. Reversible isolated sensory axonal neuropathy due to cobalamin deficiency. Muscle Nerve. 2012; 45: 428-430.

48. Tweet MS, Polga KM. 44-year-old man with shortness of breath, fatigue, and paresthesia. Mayo Clin Proc. 2010; 85: 1148-1151.

49. Carmel R. Nutritional vitamin-B12 deficiency. Possible contributory role of subtle vitamin-B12 malabsorption. Ann Intern Med. 1978; 88: 647-649.

50. Lorenzl S, Vogeser M, Müller-Schunk S, Pfister HW. Clinically and MRI documented funicular myelosis in a patient with metabolical vitamin B12 deficiency but normal vitamin B12 serum level. J Neurol. 2003; 250: 1010-1011.

51. Akdal G, Yener GG, Ada E, Halmagyi GM. Eye movement disorders in vitamin B12 deficiency: two new cases and a review of the literature. Eur J Neurol. 2007; 14: 1170-1172.

52. Lehman JS, Bruce AJ, Rogers RS. Atrophic glossitis from vitamin B12 deficiency: a case misdiagnosed as burning mouth disorder. J Periodontol. 2006; 77: 2090-2092.

53. Atanassova PA, Chalakova NT, Goranov SE, Ilieva EM, Sotirova KN, Massaldjieva RI. A case of encephalomyelopolyneuropathy in vitamin B12 deficiency. Folia Med (Plovdiv). 2004; 46: 52-54.

54. Chapuis TM, Favrat B, Bodenmann P. Cobalamin deficiency resulting in a rare haematological disorder: a case report. J Med Case Rep. 2009; 3: 80.

55. Edvardsson B, Persson S. Chorea associated with vitamin B12 deficiency. Eur J Neurol. 2011; 18: e138-139.

56. Graells J, Ojeda RM, Muniesa C, Gonzalez J, Saavedra J. Glossitis with linear lesions: an early sign of vitamin B12 deficiency. J Am Acad Dermatol. 2009; 60: 498-500.

57. Song SM, Bae KW, Yoon HS, Im HJ, Seo JJ. A case of anemia caused by combined vitamin B12 and iron deficiency manifesting as short stature and delayed puberty. Korean J Pediatr. 2010; 53: 661-665.

58. Yamada K, Shrier DA, Tanaka H, Numaguchi Y. A case of subacute combined degeneration: MRI findings. Neuroradiology. 1998; 40: 398-400.

59. Lewis AL, Pelic C, Kahn DA. Malignant catatonia in a patient with bipolar disorder, B12 deficiency, and neuroleptic malignant syndrome: one cause or three? J Psychiatr Pract. 2009; 15: 415-422.

60. Bar-Shai M, Gott D, Marmor S. Acute psychotic depression as a sole manifestation of vitamin B12 deficiency. Psychosomatics. 2011; 52: 384-386.

61. Buchman N, Mendelsson E, Lerner V, Kotler M. Delirium associated with vitamin B12 deficiency after pneumonia. Clin Neuropharmacol. 1999; 22: 356-358.

62. Al-Shubaili AF, Farah SA, Hussein JM, Trontelj JV, Khuraibet AJ. Axonal and demyelinating neuropathy with reversible proximal conduction block, an unusual feature of vitamin B12 deficiency. Muscle Nerve. 1998; 21: 1341-1343.

63. Turner MR, Talbot K. Functional vitamin B12 deficiency. Pract Neurol. 2009; 9: 37-41.

64. Reynolds EH, Bottiglieri T, Laundy M, Stern J, Payan J, Linnell J, et al. Subacute combined degeneration with high serum vitamin B12 level and abnormal vitamin B12 binding protein. New cause of an old syndrome. Arch Neurol. 1993; 50: 739-742.

65. Ilniczky S, Jelencsik I, Kenéz J, Szirmai I. MR findings in subacute combined degeneration of the spinal cord caused by nitrous oxide anaesthesia--two cases. Eur J Neurol. 2002; 9: 101-104.

66. El Otmani H, El Moutawakil B, Moutaouakil F, Gam I, Rafai MA, Slassi I. [Postoperative dementia: toxicity of nitrous oxide]. Encephale. 2007; 33: 95-97.

67. Cartner M, Sinnott M, Silburn P. Paralysis caused by "nagging". Med J Aust. 2007; 187: 366-367.

68. Shulman RM, Geraghty TJ, Tadros M. A case of unusual substance abuse causing myeloneuropathy. Spinal Cord. 2007; 45: 314-317.

69. Sethi NK, Mullin P, Torgovnick J, Capasso G. Nitrous oxide "whippit" abuse presenting with cobalamin responsive psychosis. J Med Toxicol. 2006; 2: 71-74.

70. Kumthekar AA, Gidwani HV, Kumthekar AB. Metformin associated B12 deficiency. J Assoc Physicians India. 2012; 60: 58-60.

71. Fujita H, Narita T, Yoshioka N, Hosoba M, Ito S. A case of megaloblastic anemia due to vitamin B12 deficiency precipitated in a totally gastrectomized type II diabetic patient following the introduction of metformin therapy. Endocr J. 2003; 50: 483-484.

72. Liu KW, Dai LK, Jean W. Metformin-related vitamin B12 deficiency. Age Ageing. 2006; 35: 200-201.

73. Bell DS. Metformin-induced vitamin B12 deficiency presenting as a peripheral neuropathy. South Med J. 2010; 103: 265-267.

74. Rajkumar AP, Jebaraj P. Chronic psychosis associated with vitamin B12 deficiency. J Assoc Physicians India. 2008; 56: 115-116.

75. Shiriatzadeh A, Gharegozli K. Misdiagnosis of vitamin B12 deficiency: a case report. J Neurol Sci. 2009; 285: S215.

76. Mankad K, Kullmann DM, Davagnanam I. Neurological manifestation of vitamin B12 deficiency. Am J Med. 2010; 123: e1-2.

77. Gomez-Bernal GJ, Bernal-Perez M. Vitamin bâ,â,, deficiency manifested as mania: a case report. Prim Care Companion J Clin Psychiatry. 2007; 9: 238.

78. Pacchetti C, Cristina S, Nappi G. Reversible chorea and focal dystonia in vitamin B12 deficiency. N Engl J Med. 2002; 347: 295.

79. Chatterjee A, Yapundich R, Palmer CA, Marson DC, Mitchell GW. Leukoencephalopathy associated with cobalamin deficiency. Neurology. 1996; 46: 832-834.

80. Cikrikcioglu MA, Benli AR, Erkal H, Korkmaz F, Tukek T. Masked vitamin B12 deficiency anemia as if it was haemolytic anemia. Eur J Intern Med. 2008; 19: e73-74.

81. Whyte AF, Jones DL, Dreyer MD. Vitamin B12 deficiency causing hyperhomocysteinaemia and cerebral venous sinus thrombosis. Intern Med J. 2012; 42: 601-603.

82. Bourgeois V, Desbordes M, Follet M, Haouzir S, Guillin O. Charles Bonnet syndrome and vitamin B12 deficiency: a case report. Gen Hosp Psychiatry. 2010; 32: 446.

83. Theaker JM, Porter SR, Fleming KA. Oral epithelial dysplasia in vitamin B12 deficiency. Oral Surg Oral Med Oral Pathol. 1989; 67: 81-83.

84. Pawlak R, Parrott SJ, Raj S, Cullum-Dugan D, Lucus D. How prevalent is vitamin B(12) deficiency among vegetarians? Nutr Rev. 2013; 71: 110-117.

85. McGuire S. U.S. Department of Agriculture and U.S. Department of Health and Human Services, Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, January 2011. Adv Nutr. 2011; 2: 293-294.

86. Parikh S, Matulis J. Vitamin B12 Deficiency Associated With Metformin. Endocrinologist. 2010; 20: 38-40.

87. Pawlak R, James PS, Raj S, Cullum-Dugan D, Lucas D. Understanding Vitamin B12. Am J Lifestyle Med. 2013; 7: 60-65.

88. Keller M, Redemann B, Chavez-Zander U, Leitzmann C. Effect of cyanocobalamin-fortified toothpaste on vitamin B12 status of vegetarians and vegans. Abstract presented at the 6th International Congress on Vegetarian Nutrition. Loma Linda University. 2013.

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