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Main Neurological Alterations due to Vitamin B12 Deficiency

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Abstract

Introduction: The Vitamin B12 deficiency (cobalamin) occurs due to different factors: Nutritional deficiency, inborn or acquired errors in the absorption pathways and defects in transport or metabolic pathways.

Objective: Describe the different causes of vitamin B12 deficiency and its damage to the human body, specifically neurological disorders.

Methods: Literature review on clinical aspects of vitamin B12 deficiency. 25 references were selected, published from 2009 to 2019, composed of cohort study and clinical trials, randomized clinical case studies and case control.

Results: In common sense, vegetarians are the group risk to deficiency of vitamin B12, although studies indicate a high prevalence for this deficiency in the elderly. Most cases are represented by subclinical disability. Currently, 30% to 50% are associated with food-cobalamin malabsorption. Treatment is performed intramuscularly, but there is evidence that oral replacement is also effective.

Conclusion: Because cobalamin deficiency can be confused with other pathologies, periodic laboratory tests are recommended in the elderly and patients with risk factors, even in the absence of symptoms, while for other individuals, the tests must be performed in routine exams, since the highest rate of hypovitaminosis is subclinical.

Keywords: *Vitamin B12; Vitamin B12 Deficiency; Cyanocobalamin*

Introduction

Cobalamin, also known as vitamin B12, is the term used to characterize the group of corrinoid compounds, which are substances that have cobalt in their structure. It is composed of a ribose molecule, a phosphate and a nitrogenous base (5,6-dimethylbenzimidazole) linked to the corrin ring [1]. The synthesis of cobalamin is produced exclusively by microorganisms and for this reason it is found only in foods fermented by bacteria or contaminated by them, or in animal tissues that accumulated after their acquisition through the intestinal microbiota, through the ingested diet, as long as the diet has an adequate supply of cobalt. Combs-Junior [2] highlight that in ruminants

the production is higher if the cobalt supply is sufficient for ruminal microbial synthesis, because of this, ruminants contain higher levels of cobalamin in their tissues than non-ruminant species, the authors also describe that foods of animal origin are considered good sources of vitamin B12, while those of plant origin have inexpressive amounts. We considered three works, Mahan [3] this author recommends the daily ingestion of vitamin B12 which is 2,4 µg per day for adults and the elderly, compared to Finglas [1] which described that in the elderly, due to physiological conditions, it is indicated that the majority of this amount should be obtained by B12 enriched food or by food supplements that contain B12 vitamin, due to the incapacity of the organism to disassociate the food's cobalamin or its transporting protein. Corroborating with this assertive, we highlight Combs-Júnior [2] this author points that if the intake of animal source food is scarce or restricted, it is necessary to use supplements or foods enriched with cobalamin. It is worth mentioning that B12 vitamin was described by authors such as Wong., *et al*. [4] as a micronutrient essential to human health for being primordial to the cells of the organism, for participating in diverse enzymatic activities. In humans, it develops in two crucial functions: when it is in methylcobalamin form, it acts like a coenzyme in the methylation of the homocysteine to the methionine in the cell's cytoplasm. This metabolic step is important for the synthesis of DNA. In the form of 5-deoxyadenosylcobalamin, it acts like a coenzyme in the conversion of the L-methylanomyl Coenzyme A to the succinyl coenzyme A in the mitochondria [5]. This way, Wong., *et al*. [4] reinforces that the deficiency of the cobalamin can attack several metabolic pathways simultaneously, causing a variety of signs and symptoms.

Aim of the Study

This study had as a goal the increasing in production of scientific studies surrounding the deficiency of the vitamin B12 and describing the causes of this deficiency and their possible impacts in the neurological functions to human's organisms, presenting ways in how to treat it.

Methods

To achieve the objectives of this study, it was opted for the integrative bibliographical of the literature review, for Gil (2009), a bibliographical research is developed from an already elaborated material, built mainly upon scientific articles. The integrative review makes it possible to gather and synthesize results of multiple published studies, in a systematic and orderly manner, contributing to the deepening of the theme studied. In order to identify the articles on vitamin B12 deficiency and its clinical aspects, it was conducted an online research in the database: PubMed e Google Scholar. After searching for the scientific publishing, it was made a first analysis of the articles, to verify its approximation with the proposed objectives of the study. Likewise, in order to grant its refinement, the following inclusion criteria were defined: studies in the English and Portuguese languages; published between the periods of 2009 to 2019; cohort studies and clinical trials; randomized clinical case studies; control case, bibliographical case studies were excluded, monographs, final papers. The descriptors and respective terms utilized in the search were: vitamin B12, vitamin B12 deficiency and cyanocobalamin.

Studies about individuals with cobalamin hypovitaminosis by different etiologies for inquiry of clinical aspects and treatments were prioritized. Works about hypovitaminosis not related to the vitamin B12 were also excluded.

The obtained studies occurred through careful reading of the title and abstract by the first author, verifying its adequacy to the proposed objectives and inclusion criteria. From this survey, it was possible to identify the existing studies in the bases researched in the proposed time frame, making up a total of twenty-five complete articles and available with the theme of the study. No evaluation score was applied on the quality of the articles due to the lack of this type of instrument for descriptive studies.

Finally, the articles were analyzed and the production of the results occurred descriptively, from floating readings and, then in-depth, performed by a researcher.

Results

The absorption of cobalamin in the digestive system is a complex process that requires an unharmed gastrointestinal tract. Cobalamin from the diet is linked to proteins present in food. In the stomach it is released through the action of gastric acid and pepsin and binds to haptocorrin (a carrier protein) secreted by the salivary glands and gastric mucosa. Then, in this form, it is transported to the duodenum, where haptocorrin is digested by pancreatic proteases, releasing cobalamin, which then binds to the intrinsic factor forming a complex [6]. The intrinsic factor (derived from the secretion of parietal cells from the stomach) has the function of protecting the cobalamin and transporting it to its cubilina receptor, located on the edge in the distal portion of the ileal mucosa. Absorption of this complex by the cubilina receptor is calcium-dependent [7]. Within the enterocyte, lysosomes degrade the complex by releasing cobalamin [2]. About 3 to 4 hours after it enters circulation [1]. In plasma cobalamin is transported bound to carrier proteins: 70 to 80% are bound to haptocorrin and 10 to 30% are bound to transcobalamin, which is the biologically active form of vitamin B12 absorbed by all cells [2]. Body reserve of vitamin B12 is 2 to 5 mg in adults, and 80% of this reserve is in the liver Body reserve of vitamin B12 is 2 to 5 mg in adults and 80% of this reserve is in the liver [3]. Vitamin B12 is excreted renally and bile duct, and 65 to 75% of biliary excretion are reabsorbed and again available for metabolic functions. This resorption also depends on the presence of intrinsic factor [2].

Vitamin B12 deficiency can occur due to different factors: nutritional deficit, inborn or acquired errors in the absorption pathways, and disorders in metabolic pathways or transport of cobalamin [2]. The most prevalent cause is malabsorption [7]. Vitamin B12 deficiency may occur in different age groups but have a high prevalence in the elderly. Studies indicate that vitamin B12 deficiency affects about 5% of people aged 65 - 74 years and more than 10% in people aged 75 years or older [8]. The elderly are vulnerable to develop this deficiency, due to low intake, loss of gastric function resulting from the aging process that leads to malabsorption, which results in a higher incidence of pernicious anemia. B12 deficiency in this audience is related to cognitive decline, dementia, depression and anemia [9].

A vitamin B12 deficiency may be clinical or subclinical. Clinical deficiency is the most severe form, usually caused by an error in the absorption mechanism. It may be due to deficiency of the intrinsic factor, which causes severe malabsorption, or by problems in ileum receptors. Clinical symptoms in general are present and may be severe or mild and progressive. Biochemical changes, hematological and neurological changes occur. This is a serious condition that requires medical intervention [5]. Its prevalence is low, lower than 1% in adults, and 1% to 2% in the elderly [10]. Subclinical vitamin B12 deficiency is characterized by asymptomatic patients, who nevertheless have low serum vitamin B12 levels [5]. Its etiology is usually unknown, and approximately 30% to 50% of cases were associated with food-bound vitamin B12 malabsorption. Biochemical changes occur that rarely progress to clinical deficiency [10].

Symptoms of deficiency may be gastrointestinal, hematological, and neurological. Hematological and neurological symptoms are of clinical importance, as they may be related to serious or even potentially fatal diseases. Hematological alterations are the main observable consequence of vitamin B12 deficiency but can be easily confused with folate deficiency. In both clinical situations there is interference with the normal synthesis of deoxyribonucleic acid (DNA), resulting in megaloblastic alteration, causing macrocytosis. Neurological symptoms may occur associated with hematological or independent of them. Neurological symptoms include sensory disorders in the extremities (tingling and numbness), discomfort in the lower limbs, motor disorders, including abnormal gait, cognitive alterations ranging from loss of concentration to memory loss, disorientation and weak dementia, with or without mood changes [1]. These disorders are due to the combined degeneration of the lateral and posterior funiculi of the spinal cord due to damage in the myelin sheaths [11].

Disability due to inadequate intake can occur in both vegetarians and malnourished individuals. The fact that cobalamin is found in considerable quantity in foods of animal origin, and those of plant origin are devoid of their content, makes strict vegetarians (those that exclude all animal foods from their diet) a group susceptible to deficiency of this vitamin [2]. In a study conducted with individuals who adopted different types of vegetarian diet, different stages of vitamin B12 deficiency were noted, associated with the degree of animal source foods restriction. Strict vegetarians had lower vitamin B12 levels and the others (ovo-lacto vegetarians and lactovegetarians)

presented metabolic characteristics indicating vitamin B12 deficiency, evidenced by a substantial increase in total homocysteine concentrations, which is a risk factor for cardiovascular disease [12]. This type of deficiency delays to be developed in vegetarians due to enterohepatic resorption of the vitamin, which contributes to the delay in the depletion of body stocks [13].

Malabsorption of food-bound cobalamin is the main cause of cobalamin deficiency in adults. It occurs due to the inability of the body to disassociate cobalamin from food or its carrier protein, and is due to damage to gastric parietal cells that cause gastric dysfunction or reduced gastric acid secretion or achlorhydria [14]. May be caused by gastric diseases, such as simple atrophic gastritis, in patients undergoing gastrectomy, or in patients on chronic use of antiulcer medications such as proton pump inhibitors or H_2 antagonists [2]. In this type of deficiency, a progressive and slow depletion of vitamin B12 occurs in the body, which can lead to severe hematological, psychological and neurological damage [14].

Other situations that may lead to cobalamin deficiency are the occurrence of failures in the mechanism of its absorption in intestine, resulting from pathologies such as Crohn's disease, distal ileal resection or previous ileocolonic, which cause damage to cobalamin receptors located in the ileum [15]. Chronic use of metformin, an oral hypoglycemic device extensively used in the treatment of type 2 diabetes mellitus, is also a risk factor for cobalamin deficiency. There are several hypotheses for such deficiency, but the most acceptable is that metformin interferes with the receptors cubilin, located in the ileum, responsible for the absorption of vitamin B12 [16]. Other factors that can cause cobalamin malabsorption in the gut are excessive bacterial growth in the microbiota and intestinal parasites such as fish tapeworm, which can effectively compete with the host by absorbing vitamin B12 [2].

The usual treatment used for vitamin B12 deficiency is parenteral administration of 1000 µg hydroxycobalamin or cyanocobalamin. The dose can be administered more than once a week (depending on the severity of the case) for 1 to 2 weeks and then then the same dose applied weekly until the condition improves, followed by monthly injections for maintenance. However, studies have shown that daily dietary supplementation with 1000 to 2000 µg of cyanocobalamin administered orally has been as effective as that of cobalamin administered by intramuscular injections to correct biochemical markers of vitamin B12 deficiency. The lowest dose of oral cyanocobalamin required to normalize vitamin B12 levels is more than 200 times higher than the recommended daily intake [17].

The most effective method for preventing vitamin B12 deficiency is the intake of animal source foods. This would theoretically put vegetarians at risk for such a deficiency [18]. However, studies indicate that the use of foods enriched with vitamin B12, such as breads [19] and mineral water [20] improves serum vitamin B12 levels. In cases of deficiency caused by intestinal malabsorption and ileus diseases, supplementation should be initiated before clinical manifestations occur. Individuals who make chronic use of proton pump inhibitors and metformin may benefit from the use of oral cyanocobalamin [21].

Discussion

Due to the complexity of cobalamin metabolism, its deficiency can be due to different factors: nutritional deficit and inborn or acquired errors in metabolic pathways [2]. There is a common sense that the dietary factor is the main cause of cobalamin deficiency and that vegetarians are the public at risk for it. However, several studies point to the high prevalence for this deficiency in the elderly [8]. One of the causes for the high prevalence of this deficiency in the elderly may be the physiological changes that occur in the body due to aging. These changes affect nutritional status, as appetite, salivary secretions and gastric acid are reduced, which are important components in the cobalamin absorption mechanism. The classic form of cobalamin deficiency is pernicious anemia, which is the main cause of observable symptoms. However, it currently represents a minority of diagnoses of deficiency, and the subclinical deficiency of cobalamin represents the largest number of cases. Usually its etiology is unknown. According to Carmel., *et al.* [10], 30 to 50% of cases of subclinical cobalamin deficiency are associated with food-bound vitamin B12 malabsorption, which is the main cause of cobalamin deficiency in adults. The malabsorption of vitamin B12 linked to food produces a slow and progressive depletion of cobalamin in the body and can cause a variety

of signs and symptoms. It is a common problem in different populations and is often not identified due to the clinical manifestations being subtle and confused with other pathologies pathologies. A study point out that not all patients with biochemical changes in serum vitamin concentrations had hematological or neurological alterations and the signs and symptoms presented were nonspecific [22].

The usual treatment for cobalamin deficiency is intramuscular vitamin injection, due to parenteral treatment, it quickly and reliably restores your stocks. Some studies indicate that oral treatment can be as effective as intramuscular treatment, besides offering advantages of ease of administration and lower cost. According to Eussen., *et al.* [17], the lowest dose of oral cyanocobalamin required to normalize serum cobalamin levels is more than 200 times higher than recommended in the diet, which is approximately 2.4 µg per day. Supposedly, the mechanism for the efficacy of this oral route is that free cobalamin can be absorbed both passively (without binding to the intrinsic factor) and actively (after binding to the intrinsic factor) in the terminal ileum. Passive diffusion is responsible for 1 - 2% of total absorption and is not affected in patients with pernicious anemia or gastroduodenal surgical resection [23].

Considering that cobalamin participates in the synthesis of DNA and red blood cells, which is important in the maintenance of the myelin sheath, a protective covering that surrounds nerve fibers, its deficiency can affect the hematological system and nervous system. The impact of this deficiency on nerve cells, spinal cord and brain can be potentially serious. Cobalamin is also involved in the metabolic process of elimination of homocysteine. Elevated homocysteine levels increase the risk of cardiovascular disease. Therefore, the importance of this vitamin in the health of individuals should not be neglected, and its state should be periodically evaluated in risk groups. Further studies are needed to clarify the absorption and metabolism of vitamin B12, especially studies related to subclinical deficiency and food-related deficiency, since most cases of vitamin B12 deficiency are related to them, whose etiology is unknown [24,25].

Conclusion

Vitamin B12 is a crucial micronutrient to human health because it is essential to cellular metabolism. Its deficiency can cause potentially serious long-term damage, especially in the nervous system. Because the initial symptoms of deficiency are nonspecific and subtle, they are easily confused with other pathologies. Periodic laboratory tests are recommended for the detection of vitamin deficiency (preferably vitamin B12 and homocysteine dosage and if possible methylmalonic acid). Examinations should be performed in populations at risk, even in the absence of symptomatology: individuals with gastric or intestinal diseases, gastric or intestinal resection, chronic metformin, proton pump and anti-H_2 inhibitors users, vegetarians and the elderly. For the other patients, serum vitamin B12 dosage is recommended in routine examinations. Early diagnosis allows the correction of serum cobalamin levels, avoiding the progression of deficiency and future damage to the body.

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