IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 9 Ser.3 (September. 2023), PP 61-65
www.iosrjournals.org

Neurological aspects of vitamin B12 deficiency: metabolism, pathophysiology, diagnosis and management.

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Abstract :
Vitamin B12 deficiency, whether due to intake or malabsorption, mainly manifests itself as macrocytic anemia with the presence of bone marrow megaloblasts. Clinical signs other than those induced by anemia may be associated, including glossitis and neurological disorders. The severity of this deficiency depends on these neurological manifestations. They are polymorphous, ranging from the typical picture of combined sclerosis of the spinal cord to sensory neuropathy, optic neuropathy, damage to the cranial pairs, cognitive disorders and even dysautonomia. Diagnosing and managing these disorders has a major impact on subsequent prognosis. In this mini-review, we will present the neurological picture of this deficiency, detailing its diagnosis and therapeutic management.

Key words*: Vitamin B12, neurological aspects, diagnosis, management.*

Date of Submission: 06-09-2023 Date of Acceptance: 16-09-2023

I. Introduction:

The human body needs vitamins to maintain good health. There are 13 vitamins, with a wide variety of roles: either genomic action by direct binding to a nuclear receptor, or co-enzyme function, or group transport, or antioxidant action [1].

Vitamins have no energetic value, but they are necessary for humans who cannot synthesize them in sufficient quantities. They are supplied by the diet. If these needs are not met, a state of "deficiency" sets in. Vitamins are divided into two groups: "fat-soluble" vitamins (A, D, E, K), and "water-soluble" vitamins (vitamin C and group B vitamins). Diagnosis is based on blood levels of the vitamin and/or one of its metabolites. Among the group B vitamins, vitamin B12 or Cobalamin is essential for the development and proper functioning of the brain [2]. It is involved in a number of biochemical reactions, including the Kreps cycle (conversion of Methyl Malonate to Succinyl CoA), and synthesis of Methionin from Homocystein. It also plays a crucial role inDNA and RNA methylation, and is involved in epigenetic regulation [3].

Vitamin B12: General context

Vitamin B12 deficiency is a frequent and potentially serious disorder.

Deficiencies are often under-diagnosed. Symptoms may develop insidiously, or be atypical or frustrating clinical manifestations, leading to misdiagnosis.

Vitamin B12 deficiency can be the source of potentially severe clinical manifestations, including haematological and neurological complications. Management of these complications essentially involves parenteral supplementation, as in the case of neurological disorders, or if the physician doubts the patient's compliance [4].

Vitamin B12 intakes, reserves and absorption:

Vitamin B12 is only synthesized by bacteria and comes from animal products (offal, meat, eggs and dairy products). The recommended dose is 2 mg/day. It is stored in the liver for up to 1000 days. This storage would explain the diagnostic difficulty of the serum dosage, which can be normal [5].

Its absorption involves two distinct systems [5]:

The first, dependent on the intrinsic factor, is said to be specific and efficient, but is saturable as it dependson the binding of the vitamin B12-intrinsic factor complex to the ileal cell.

The second, independent of intrinsic factor, allows absorption by simple diffusion (only 1 to 5% of theingested dose). This system is non-saturable, opening up the possibility of oral substitution.

Several thresholds and definitions are proposed to define a state of vitamin B12 deficiency:

A serum level below 200 pg/ml on two samples [6].A serum level below 160 pg/ml on one sample [7].

A serum level below 200 pg/ml associated with a Homocysteine level below 13 p mol/ l [8].

A serum level below 200 pg/ml with clinical neurological signs and/or haematological abnormalities [9]. Thedefinition we will use in this work.

Physiopathology of vitamin B12 deficiency:

Vitamin B12 is abundantly stored in the human body, which explains the often delayed and insidious onset of clinical signs associated with its deficiency [10]; but also the great disparity observed between profound biological anomalies and rather discreet clinical signs [11]. Vitamin B12 is a coenzyme involved in a large number of intra-cellular enzymatic reactions [12]. These reactions enable the synthesis of DNA and methionine from homocysteine [13]. This physiological state explains the majority of disorders (haematological and mucocutaneous) associated with vitamin B12 deficiency. However, the pathophysiological mechanisms involved in neurological disorders are complex and poorly understood. One theory is based on impaired methionine synthesis, leading to a defect in the synthesis of a basic myelin protein [14]. This mechanism would be independent of any vitamin B12 enzymatic activity [15]. The resulting hyper-homocysteinemia is a vascular risk factor and may be linked to ischemic stroke and/or cognitive impairment. In addition, the "Folate Trap" theory is said to aggravate neurological disorders. Folate intake would mobilize the last stocks of vitamin B12 in Favor of the haematological line and in disfavor of the nervous system, favoring nucleic acid synthesis to the detriment of Methionine, and therefore Myelin [5].

Causes of vitamin B12 deficiency:

This deficiency is rarely due to a lack of intake. In fact, a varied diet is rich in vitamin B12. However, ingesting foods rich in vitamin B12 does not guarantee its metabolism in the body. As a result, deficiency is often linked to the syndrome of non-dissociation of vitamin B12 from its carrier proteins, at two levels: the gastric phase (due to reduced gastric secretion), or the intestinal phase (due to exocrine pancreatic insufficiency). The main causes of this syndrome [16] are pathologies responsible for disrupting the integrity of the transport system. Atrophic gastritis is the main cause, with or without Helicobacter pylori infection. Other identified causes are: pancreatic insufficiency (alcohol abuse, cystic fibrosis), gastric achlorydria (absence of gastric acid), gastrectomy, gastric bypass, certain anti-diabetic drugs (Biguanides) and proton pump inhibitors [17]. Apart from this syndrome, other causes are incriminated, such as Biermer's disease (also called pernicious anemia) with absence of intrinsic factor secretion. This condition accounts for 20-50% of causes of vitamin B12 deficiency [18]. Vitamin B12 malabsorption is another frequently reported cause. It is linked to chronic pancreatitis, pancreatectomy, gastrectomy and/or surgical resection of the gastrointestinal tract.

Non-neurological symptoms:

The main clinical and biological symptoms are summarized in Table 1. They can be clinically highly variable and vary in severity.

Haematological abnormalities are the most common. The most common is megaloblastic anaemia with macrocytosis (mean corpuscular volume greater than 110 micrometers), normochromia and medullary megaloblastosis.

Vascular manifestations linked to hyperhomocysteinemia secondary to deficiency. This is an independent risk factor for venous thromboembolic disease in particular. Homocysteine has a pro-coagulant action on endothelial cells [20].

Stomatological manifestations include Hunter's glossitis. This is a classic and frequent sign of vitamin B12 deficiency.

Clinical symptoms	Type of disorders observed
Haematological	Megaloblastic anaemia Thrombocytopenia Leukopenia Pancytopenia
Vascular	Deep-vein thrombosis
Stomatological	Hunter's Glossitis Oral mucosal erosions
Others	Hypofertility Abortions

Table 1 summarizes the non-neurological clinical manifestations of vitamin B12 deficiency.

Neurological syndromes linked to vitamin B12 deficiency:

The neurological symptoms associated with vitamin B12 deficiency are extremely polymorphous. The neurological clinical picture may be inaugural, posing a real diagnostic challenge, especially in the absence of haematological manifestations [22]. Indeed, anaemia and macrocytosis may be absent in a third of reported cases [23]. Some manifestations are suggestive, such as combined spinal cord sclerosis (CSCS) and sensory neuropathies (SN). Other symptoms are rarer and often unrecognized, and include cognitive disorders, abnormal movements and dysautonomic signs [24,25]. There are also increasing reports of neuropsychiatric symptoms which may be indicative of the disease [26].

Several studies in North African have investigated the neurological manifestations associated with vitamin B12 deficiency. A 1st Algerian series involving 43 observations [27] found CSCS in 60% of cases, SN in 65%, encephalitis in 16% and optic neuropathy in 37%. The main aetiology identified was Biermer's disease (67%). A 2nd Algerian series, involving 30 cases, also found CSCS in 43% of cases, SN in 40% of patients, isolated proprioceptive ataxia in 13.3% of cases and isolated cerebellar ataxia in one patient (3.3%). A series of 15 patients hospitalized in our department, the neurology department of the Mustapha Bacha university hospital in central Algiers (unpublished series) also found CSCS to be the main neurological manifestation. The clinical data from this series are summarized in Table 2.

Starting mode	Progressive	12 cases
	Subacute	2 cases
	Acute	1 case
Neurological examination	Posterior cord syndrome	13 cases
	Pyramidal syndrome	7 cases
	Peripheral neurogenic syndrome	7 cases
	Optic nerve involvement	1 case
Clinicl picture	CSCS	7 cases
	Sensory polyneuropathy	5 cases
	Acute Polyradiculonevritis	1 case
	Optic neuritis	1 case
Somatic examination	Mucocutaneous heat	5 cases
	Depilated tongue	5 cases
	Normal	5 cases

Table 2 summarizing the clinical aspects of our series (Kediha and al).

1/ Combined sclerosis of spinal cord:

This is a classic neurological manifestation of vitamin B12 deficiency. Clinically, CSCS is fairly well defined. It is accompanied by dysesthesia, deep sensory disturbance with impaired segmental position sense and/or spastic para- or tetra-paresis. Neuropathologically, there is multifocal axonal loss and segmental demyelination, with more severe involvement of the cervical and thoracic spinal cord, progressively affecting the posterior columns, followed by the anterolateral tracts [29]. These neuropathological lesions are associated with overproduction of Tumor Necrosis Factor Alpha (TNF alpha) and reduced synthesis of two neurotrophic agents: Epidermal Growth Factor (EGF) and Interleukin 6 (IL6), caused by vitamin B12 deficiency [30]. MRI shows lesions classically involving the posterior and lateral columns, leading to lower and upper limb involvement [31].

CSCS clinically associates a pyramidal syndrome and a posterior cord syndrome, with proprioceptive ataxia and paresthesias in the foreground. Paresthesias are often reported several months before deep sensitivity disorders. Often, only an isolated Babinski sign is found, suggestive of pyramidal syndrome [32]. Motor deficits

are rare, occurring only in advanced forms or those diagnosed later.

2/ Peripheral neuropathies:
Peripheral manifestations are also very frequent (20-70% depending on the series). They may be isolated or associated with other central neurological signs, such as CSCS [29]. This neuropathy may be purely sensory or sensory motor, of axonal type. It may be clinically asymptomatic, and only visible on electromyography.

3/ Cognitive and psychiatric features:
They are polymorphous, involving memory disorders, sometimes with a genuine dementia syndrome, personality changes, psychotic states, emotional lability and, rarely, delirium. All these disorders can be seen without any hematological manifestations or low vitamin B12 levels [33].

4/ Optic neuritis:
They are usually bilateral, affecting central vision, with or without optic atrophy [32].

5/ Other symptoms:
Cerebellar involvement can be observed from the onset of neurological symptoms [34], as can involvement of the cranial pairs, Parkinsonism or abnormal movements. Dysautonomic involvement is seen in 22% of cases, and is inaugural in one out of two cases, in the form of arterial hypotension or genital-sphincter disorders.

Evolution of neurological disorders:
Three factors appear to play a role in the improvement of neurological symptoms: severity of symptoms at diagnosis, duration of disease evolution and high haematocrit levels [34]. Moreover, symptoms beginning with sensory disorders seem to recover more rapidly than those beginning with motor disorders. It should also be noted that the duration and degree of neurological improvement correlate with the duration of symptoms prior to the start of vitamin supplementation, which should therefore be started as early as possible [34].

Treatment of vitamin B12 deficiency:
Once vitamin B12 deficiency has been diagnosed, the aim of supplementation is not only to improve or even cure the signs and symptoms of deficiency, but also to replenish the body's reserves. Basic treatment is based on vitamin B12 supplementation. Intra-muscular administration is preferred, especially for neurological forms. Monitoring of the therapeutic response is based on increasing vitamin B12 blood levels, and improving haematological disorders. Intra-muscular vitamin B12 is available in the form of CyanoCobalamine, Hydroxy Cobalamine or Methyl Cobalamine [37]. In Algeria, only CyanoCobalamine is marketed. The recommended dosage is 1000 micrograms per week for one month, then 1000 micrograms per month over the long term [38].

II. Conclusions:

The neurological manifestations of vitamin B12 deficiency are highly variable, polymorphous and sometimes atypical. Vitamin B12 assays should be performed systematically in the presence of any clinical neurological picture, whether central or peripheral. However, a normal level does not rule out the diagnosis. Other tests are required to refine the diagnosis. These patients should be managed as early as possible.

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