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VITAMIN B12 DEFICIENCY WITH MULTIPLE SCLEROSIS-LIKE NEUROLOGICAL CLINICAL FRAMEWORK

PASQUALE MANSUETO*, LAURA DI STEFANO*, ALBERTO D'ALCAMO*, AURELIO SEIDITA*, FLORIANA ADRAGNA*, GIUSEPPE DRAGO*, FRANCESCO ZAPPALÀ*, MARCO AFFRONTI*, GIOVAMBATTISTA RINI*, ANTONIO CARROCCIO**
*Internal Medicine, Department of Internal and Specialistic Medicine, University Hospital of Palermo, Italy
**Internal Medicine, Hospital of Sciacca, Agrigento, Italy

[Deficit di vitamina B12 con quadro clinico neurologico simil sclerosi multipla]

SUMMARY

A severe cobalamin (vitamin B12) deficiency can occur with several disorders, involving different organs and systems, including blood, bowel, nervous system and eyes. Although most important features characterizeing this deficiency are usually haematological ones, presence of neurological involvement, in absence of blood count alterations, was just described in literature. Here we reported the case of a forty-eight years old male, suffering from celiac disease for, approximately, 5 years, vegetarian, which was admitted to our Department, referring dysesthesia of left lower limb, decreased libido and erectile dysfunction. Vitamin B12 deficiency was proved, even in absence of blood count alteration, and treated with vitamin supplement, resulting in complete remission of symptoms.

Key words: cobalamin (vitamin B12) deficit, leukoencephalopathy, vitamin supplements

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Introduction

A severe cobalamin (Cbl, vitamin B12) deficiency can occur with several disorders, involving different organs and systems, including blood, bowel, nervous system and eyes[1-4]. Although most of patients have predominant haematological manifestations, presence of neurological involvement, in absence of blood count alterations, was just described in literature.

Moreover, a folic acid supplement increases the risk of purely neurological presentation, because it masks the hematological effects of vitamin B12 deficiency. First neurologic onset is represented by numbness and limbs tingling, followed by progressive spastic paresis and ataxia.

Perception of deep touch, pressure and vibration are generally reduced, Babinsky and Romberg signs may be positive, and, finally, evoked potential tests are, sometimes, abnormal. Possible, although rare, are signs of cerebellum dysfunction, peripheral neuropathy, sphincter disturbances, optic atrophy and orthostatic hypotension[5-9].

Histological demyelinating lesions can be pointed out, followed by axonal degeneration and neuronal death, mainly interesting posterior and lateral cords of the spinal cord. Rare involvement of peripheral nerves, brain cortex and cerebellum may be demonstrated too. The lesions are visible as multiple hyperintense areas in T2-MRI[10,11]. Neurologic disorders completely regress after Cbl administration[12,13].

In this report, we describe the case of a vegetarian man aged 48, suffering from celiac disease, under gluten-free diet, affected with hypovitaminosis B12-related multiple sclerosis-like neurological manifestations, in absence of hematological disorders and/or other symptoms or signs of organ distress.

Case report

A forty-eight years old man, suffering from celiac disease for, approximately, 5 years, under gluten-free diet, and vegetarian for more than 10 years, was admitted to our Department, in February 2006, referring dysesthesia, starting from the left inguinal region and spanning the entire ipsilateral lower limb for about seven months, followed, after five months, by decreased libido and erectile dysfunction.

In November 2000, due to familiar detection of celiac disease (brother and nephew), the patient underwent antitransglutaminase and antiendomysial antibody assay and upper endoscopy, with duodenal biopsy, which supported celiac disease diagnosis. Therefore, patient started a gluten-free diet and underwent to periodical outpatient follow-up, which showed good general clinical condition, no abnormalities in physical examination, normal routine blood chemistry, except for slightly increased transaminases, hyposideremia and hypoferritinemia. Adherence to gluten-free diet led to negativity of serological assay for antitransglutaminase and antiendomysial antibodies.

In June 2005, he reported the onset of numbness, described as "*pulse-vibration*", from the left groin, extending to the entire ipsilateral lower extremity, followed, in November of the same year, from decreased libido and erectile dysfunction. Nothing notable was founded during physical examination, except for neurological examination, which showed asymmetry of tendon reflexes, more vivid on the right. For this reason, a brain MRI with intravenous contrast, which documented "multiple periventricular and subcortical hyperintense lesions", and a full spine MRI with intravenous contrast, with detection of "hyperintensities at the level of D9-D10, disc protrusions at L3-L4 and L4-L5", were performed. The reports suggested a "demyelinating leukoencephalopathy" diagnosis.

In February 2006, patient was admitted to the "Centre for Studies of Multiple Sclerosis" in Gallarate (Varese, Italy), where blood tests were performed, results all within the normal ranges, except for hypovitaminosis B12 (51 pmol/L, normal range 156-672 pmol/L) and hypercholesterolemia. In addition, the patient underwent to ECG, acoustic, visual and somatosensory evoked potentials, and cerebrospinal fluid examination, all proving within normal limits. Due to negativity of cerebrospinal fluid data, which did not support the demyelinating leukoencephalopathy diagnosis, "multifocal leukoencephalopathy under clinical surveillance, in patient affected with celiac disease, hypovitaminosis B12, and dyslipidemia" was diagnosed. Low-dose *per os* vitamin B12 treatment was recommended, as well as brain and spinal cord control MRI with intravenous contrast after 6 months, echocolordoppler imaging of carotid vessels, and gastroenterological and andrological visits in reference centers.

The same month the patient was admitted to our outpatient to perform upper endoscopy, with duodenal and gastric biopsies (hiatal hernia and chronic atrophic gastritis were pointed out) and high-dose intramuscolar vitamine B1, B6 and B12 complex therapy was prescribed three times a week. Moreover, he underwent sacral somatosensory evoked potentials test, with evidence of abnormalities. After administration of 4 doses of intramuscolar vitamine B1, B6 and B12 complex, approximately one week later, the patient reported mild dysesthesias disappearance, recovery of libido and recapture of erectile function. This confirmed the therapy and, moreover, folic acid, 15mg/day *per os*, was added. Twenty days after, when administration of 11 doses of intramuscolar vitamine B1, B6 and B12 complex had been already performed, therapy was changed, lowering to 1 vials/week of intramuscolar vitamine B1, B6 and B12 complex, and folic acid 15mg/2 days a week. Vitamin B12 assay was performed after 45 days of treatment, showing values >1200 pg/ml (normal range 174-878 pg/ml). Patient is still in follow-up in our Department, according vitamin supplement treatment to vitamin B12 and folate sierologic values and occasional reported dysesthetic disturbances.

Discussion

Correct approach to hypovitaminosis B12-related neurological presentation includes, first of all, accurate identification of the anatomical site of injury in order to reduce the broad etiology list. Dysesthesia, presenting symptom in our report, may be the result of injury in the parietal cortex, deep white matter, thalamus, brain stem, spinal cord, spinal nerves and peripheral nerves. Brain and spinal cord MRI with intravenous contrast allowed, in our case, identification of damage as "multifocal leukoencephalopathy" or "white matter disease".

The latter was first classified, according to histopathological criteria, in demyelinating (charac-

terized by destruction of the myelin sheath, by a myelinoclastic process), dysmyelinating (usually metabolic, centred on the unusual nature of myelin content), hypomyelinating (marked by a reduced production of myelin) leukoencephalopathies and encephalopathies (associated with myelin cystic degeneration). Pathogenic considerations joined histopathological classification, and, to date, it must be considered acquired and connatal (also known as "leukodystrophies") leukoencephalopathies.

The former, predominantly demyelinating, are associated with late, or at least delayed onset, than connatal variety. The main etiologic factors, responsible for the histopathologic changes, are reported in Table 1[14-16].

I. Non infectious inflammatory disorders character
• Multiple sclerosis and its variants • Acute Disseminated Encephalomyelitis (ADEM)
II: Infectious-inflammatory disorders
• Congenital CMV infection • CMV subacute encephalitis • HIV subacute encephalitis • Subacute sclerosing panencephalitis • Progressive multifocal leukoencephalitis • Other infections
III. Hypoxic-ischemic disorders
• Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) • Periventricular leukomalacia • Polycystic leukoencephalopathy • Delayed hypoxic-ischemic demyelination • Subcortical arteriosclerotic encephalopathy (Biswanger disease) • Aging • Vasculitis (in the course of systemic lupus erythematosus, Bechet's disease, etc.) • Radiations
IV. Post-traumatic
• Oedematous • Post-radiation
V. Other

Table 1: pathophysiological classification of white matter disease

In our case, excluding primary hypothesis of multiple sclerosis demyelinating multifocal leukoencephalopathy, given negative cerebrospinal fluid examination, and founding severe hypovitaminosis B12, a likely vitamin deficiency origin of neural abnormalities was supposed. Although in many patients affected with Cbl deficiency haematological manifestations, variously associated with gastroenterological, neurological and psychiatric ones, are predominant, a purely clinical neurological presentation, with no deteclable abnormalities in cell blood count, has just been described in literature. In this regard, it should be pointed out as a folate supplement can mask hematologic effects of vitamin B12 deficiency, increasing the risk of neural damage and resulting neurological onset[17,18].

Daily minimum vitamin B12 requirement is 2.5μg/day, the only source from animal products. The body stores, mainly in the liver, amounted to 3-5mg and, therefore, clinical signs of vitamin introduction deficiency or malabsorption appear only after a period ranging from 2 to 5 years. In the stomach, Cbl contained in food is released, by the action of pepsin and gastric acid, and forms a complex with the aptocorrina, a glycoprotein secreted in saliva. In duodenum, pancreatic proteases degrade aptocorrina, releasing Cbl, which can, then, bound intrinsic factor (IF), a glycoprotein produced by gastric parietal cells. The complex Cbl-IF reaches terminal ileum, where it binds to specific receptors (cubiline) present within enterocytes brush border. After endocytosis, the complex enters the cells, IF is degradated and Cbl bind to transcobalamin (TCII), and, finally, enter the portal circulation. Once binding by specific cells receptors, TCII-Cbl complex is degraded and Cbl released into the cytoplasm. In humans there are 2 metabolically active Cbl forms: methylcobalamin and adenosylcobalamin. The former is required for methionine synthase, which catalyses the homocysteine conversion to methionine. The latter, however, is necessary for the methylmalonyl-CoA conversion to succinyl-CoA. Reduction of first metabolic way, which cooperates with folate, results in a S-adenosylmethionine deficiency, which reduces methylation of cytosine and thymidine acid, and cause erroneous DNA incorporation of uracil instead of thymine. Reduced DNA synthesis generates megaloblasts, and reaction blocking cause accumulation of homocysteine too. A reduced activity of the second pathway results in an increase of methylmalonyl-CoA and its hydrolysis product (i.e. methylmalonic acid), and a reduced succinate availability[1-4,19-21]. The most important causes of vitamin B12 deficiency are listed in Table 2.

To date, pathogenesis of neurological disorders in patients affected with Cbl deficiency has not been elucidated. Some authors argue that neurological damage can be attributed, at least in part, to methionine deficient synthesis. Further evidences pointed

out abnormal methylmalonyl-CoA and its precursor (i.e. propionyl-CoA) storage in the tissues, with effects on myelin fatty acid synthesis. A new hypothesis considered Cbl deficiency-induced abnormal synthesis of certain cytokines: as a matter of fact, tumor necrosis Factor (TNF), which proved to have lytic effect on myelin, is increased in cerebrospinal fluid of experimental animals previously gastrectomized to cause Cbl deficiency. In these studies, neurological lesions were prevented by intrathecal injection of anti-TNF antibody or neurotrophic cytokines, such as epidermal growth factor (EGF) or interleukin (IL)-6. Similarly, in serum of Cbl deficiency patients, an increase of TNF and a decrease of EGF concentrations were demonstrated, both regressed after vitamin B12 administration[19-22].

I. Inadequate intake: vegetarians "vegans" (rare)
II: Malabsorption
A. Altered release of cobalamin from food:
• Gastric achlorhydria
• Partial gastrectomy
• Gastric secretion blocking drugs
B. Insufficient production of intrinsic factor:
• Pernicious anaemia
• Total gastrectomy
• Intrinsic factor congenital absence or malfunction (rare)
C. Diseases of the terminal ileum:
• Tropical sprue
• Non-tropical sprue
• Regional enteritis
• Granulomatous disorders (rare)
• Malignancies
• Bowel resection
• Imerslund-Grasbeck syndrome (rare)
D. Competition for cobalamin:
• Parasitism (i.e. tapeworms)
• Small intestinal bacterial overgrowth
E. Iatrogenic:
• p-aminosalicylic acid
• Colchicine
• Neomycin
III. Other causes
• Trancobalamin II deficit
• Congenital enzyme deficiencies
• Nitrous oxide anesthesia

Table 2: vitamin B12 deficiency causes

Although Cbl deficiency present, primarily, with degeneration of posterior and lateral cords of spinal cord, thus causing symptoms/signs of peripheral neuropathy, it is possible, although rare, involvement of peripheral nerves, cerebral cortex, and, more rarely, cerebellar cortex. In early stages, demyelinating lesions, visible as multiple hyperintense areas on T2-MRI, represents the histological framework. These are followed by axonal degeneration and, finally, by irreversible neuronal death. The earliest neurologic manifestations are represented by numbness and tingling in the limbs, followed by progressive spastic paresis and ataxia.

Pulse, position and kinetic sensitivity are generally reduced, Babinski and Romberg signs can be positive, and evoked potentials are often abnormal. Possible, although rare, are signs of cerebellar dysfunction, peripheral neuropathy, sphincter disturbances, optic atrophy and orthostatic hypotension[5-11].

In our case, the rapid disappearance of neurological symptoms following treatment with vitamin B12 supplement confirms the hypothesis of "deficiency leukoencephalopathy". The mainstay of vitamin B12 deficiency treatment is replacement, preferring parenteral administration, it being generally linked to absorption defect. The dosage should be adequate to vitamin B12 levels and patient clinical manifestation, with an usual initial parenteral treatment of 1000μg of Cbl for 8 weeks, followed by 1000μg of Cbl per month for life. The response is usually quick and satisfactory, with resolution of haematological disorders and alleviation or disappearance of neurological symptoms, although the latter are not always reversible[12,13].

In our patient, according to the reported history of long-term vegetarianism and the proved anti-transglutaminase and antiendomysial antibody negativity in all the controls after 2004, so excluding malabsorption from active celiac disease, hypovitaminosis primary cause was likely attributable to an employment deficit[23,24]. Moreover, the intake of vegetable foods, with high folate shares, may have influenced the absence of detectable haematological abnormalities[18].

In conclusion, here we described a multiple sclerosis-like neurological presentation of hypovitaminosis B12 in a vegetarian patient affected with celiac disease, his, MRI documented, neurological lesions, in absence of alterations in blood count, and his successfully treatment with parenteral administration of vitamin B12 supplement.

References

1) Herrmann W, Obeid R. *Cobalamin deficiency*. Subcell Biochem 2012; 56: *301-22*.
2) Langan RC, Zawistoski KJ. *Update on vitamin B12 deficiency*. Am Fam Physician 2011; 83: *1425-30*.
3) Quadros EV. *Advances in the understanding of cobalamin assimilation and metabolism*. Br J Haematol 2010; 148: *195-204*.
4) Solomon LR. *Disorders of cobalamin (vitamin B12) metabolism: emerging concepts in pathophysiology, diagnosis and treatment*. Blood Rev 2007; 21: 113-30.
5) Shevell MI, Rosenblatt DS. *The neurology of cobalamin*. Can J Neurol Sci 1992; 19: *472-86*.
6) Savage DG, Lindenbaum J. *Neurological complications of acquired cobalamin deficiency: clinical aspects*. Baillieres Clin Haematol 1995; 8: *657-78*.
7) Gadoth N, Figlin E, Chetrit A, Sela BA, Seligsohn U. *The neurology of cobalamin deficiency in an elderly population in Israel*. J Neurol 2006; 253: *45-50*.
8) Morita S, Miwa H, Kihira T, Kondo T. *Cerebellar ataxia and leukoencephalopathy associated with cobalamin deficiency*. J Neurol Sci 2003; 216: *183-4*.
9) Saperstein DS, Wolfe GI, Gronseth GS, Nations SP, Herbelin LL, Bryan WW, Barohn RJ. *Challenges in the identification of cobalamin-deficiency polyneuropathy*. Arch Neurol 2003; 60: *1296-301*.
10) Karacostas D, Artemis N, Bairactaris C, Tsitourides I, Milonas I. *Cobalamin deficiency: MRI detection of posterior columns involvement and posttreatment resolution*. J Neuroimaging 1998; 8: *171-3*.
11) Kalita J, Misra UK. *Vitamin B12 deficiency neurological syndromes: correlation of clinical, MRI and cognitive evoked potential*. J Neurol 2008; 255: 353-9.
12) Carmel R. How *I treat cobalamin (vitamin B12) deficiency*. Blood 2008; 112: *2214-21*.
13) Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. *Oral versus intramuscular cobalamin treatment in megaloblastic anemia: a single-center, prospective, randomized, open-label study*. Clin Ther 2003; 25: *3124-34*.
14) Edwards MK, Smith RR. *White matter diseases*. Top Magn Reson Imaging 1989; 2: *41-8*.
15) O'Riordan JI. *Central nervous system white matter diseases other than multiple sclerosis*. Curr Opin Neurol 1997; 10: *211-4*.
16) Lyon G, Fattal-Valevski A, Kolodny EH. *Leukodystrophies: clinical and genetic aspects*. Top Magn Reson Imaging 2006; 17: *219-42*.
17) Osimani A, Berger A, Friedman J, Porat-Katz BS, Abarbanel JM. *Neuropsychology of vitamin B12 deficiency in elderly dementia patients and control subjects*. J Geriatr Psychiatry Neurol 2005; 18: *33-8*.
18) Carmel R. *Does high folic acid intake affect unrecognized cobalamin deficiency, and how will we know it if we see it?* Am J Clin Nutr 2009; 90: *1449-50*.
19) Metz J. *Pathogenesis of cobalamin neuropathy: deficiency of nervous system S-adenosylmethionine?* Nutr Rev 1993; 51: *12-5*.
20) Carmel R, Melnyk S, James SJ. *Cobalamin deficiency with and without neurologic abnormalities: differences in homocysteine and methionine metabolism*. Blood 2003; 101: *3302-8*.
21) Tanpaiboon P. *Methylmalonic acidemia (MMA)*. Mol Genet Metab 2005; 85: *2-6*.
22) Peracchi M, Bamonti Catena F, Pomati M, De Franceschi M, Scalabrino G. *Human cobalamin deficiency: alterations in serum tumour necrosis factor-alpha and epidermal growth factor*. Eur J Haematol 2001; 67: *123-7*.
23) Lindfors K, Koskinen O, Kaukinen K. *An update on the diagnostics of celiac disease*. Int Rev Immunol 2011; 30: *185-96*.
24) Caja S, Mäki M, Kaukinen K, Lindfors K. *Antibodies in celiac disease: implications beyond diagnostics*. Cell Mol Immunol 2011; 8: *103-9*.

Request reprints from:
Prof. PASQUALE MANSUETO
Dipartimento di Medicina Clinica e delle Patologie Emergenti
Azienda Ospedaliera Universitaria Policlinico 'P. Giaccone'
Via del Vespro, 141
90127 Palermo
(Italy)