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HIGH-FOLATE-LOW-VITAMIN B12 INTERACTION SYNDROME

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ABSTRACT

Introduction: Vitamin B12 deficiency is characterised by haematological and neurological complications, from mild symptoms (e.g. fatigue and paraesthesia), to severe symptoms (e.g. pancytopenia and combined degeneration of the spinal cord). If treatment is delayed, irreversible neurological damage may occur. Thus, early recognition and prompt corrective therapy are essential. The vitamin B12 deficiency can be due to a variety of anomalies: the paradoxical interaction between folic acid and vitamin B12 has recently been well described.

Case description: We report the case of a patient who presented to the emergency department with balance disorders and a blood count indicating macrocytosis. Vitamin B12 deficiency and a high folate value were detected, supporting the hypothesis of the high-folate-low-vitamin B12 interaction as a cause of vitamin B12 depletion.

Discussion: An excessive oral intake of folic acid leads to a reduction in the active fraction of vitamin B12 and this decrease exacerbates the deficiency itself. The neurological signs and symptoms of vitamin B12 deficiency are due to demyelination of the posterior and lateral columns of the spinal cord. This patient had been taking folic acid for 30 years and the serum folate value was high. We hypothesise that the high-folate-low-vitamin B12 interaction represents the cause of vitamin B12 depletion in this patient.

Conclusion: All the patients with neurological signs and symptoms should be tested for possible vitamin B12 deficiency: early diagnosis and treatment could stop the progression of the disease and allow the regression of the neurological deficit. It is important not to rely on blood count values to diagnose a vitamin B12 deficiency as the neurological and haematological outlook may be inversely proportional. This study is the first to report a case of combined sclerosis and high-folate-low-vitamin B12 interaction from Italy and is therefore of interest to public health decision makers and clinical practice.

KEYWORDS

Folate, vitamin B12 deficiency, combined degeneration, macrocytosis, ataxia

LEARNING POINTS

- Vitamin B12 and folate should be measured in all patients with neurological symptoms.
- In case of vitamin B12 deficiency, folate levels should always be measured as well.
- Vitamin blood levels should be checked periodically while taking vitamin supplements.

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INTRODUCTION

The metabolically active forms of vitamin B12, a water-soluble vitamin, are methyl- and 5'-deoxyadenosylcobalamin. In the absorption of vitamin B12, gastric acidity and pepsin allow the binding of vitamin B12 to haptocorrin. The subsequent duodenal alkaline environment favours the breaking of the vitamin B12–haptocorrin bond and the establishment of a new bond between vitamin B12 and intrinsic factor. It is intrinsic factor that allows the entry of vitamin B12 into the enterocyte. In addition, transcobalamin I and II enable the transport of vitamin B12 to tissues.

In the form of methylcobalamin, vitamin B12 promotes the conversion of homocysteine to methionine via the enzyme homocysteine methyltransferase. In this enzymatic reaction, methyltetrahydrofolate is also converted to tetrahydrofolate.

A decrease in tetrahydrofolate and its derivative, methylenetetrahydrofolate, causes a block in the enzymes that require these two compounds, resulting in dysfunction of the metabolic pathways that produce purines and deoxythymidine monophosphate.

In the form of deoxyadenosylcobalamin, vitamin B12 intervenes in conversion of methylmalonyl-CoA to succinyl-CoA via the enzyme methylmalonyl-CoA mutase and in the synthesis of 2-deoxyribonucleotides.

Since the absorption and metabolism of vitamin B12 is very complex, an alteration in any of the related steps can lead to a deficiency. Deficiency can be due to a congenital metabolic alteration or acquired from illness, drugs or eating habits. Moreover, vitamin B12 deficiency is the most common dietary deficiency in the USA. Deficiency is characterised by haematological and neurological complications, from mild symptoms such as fatigue and paraesthesia, to severe symptoms such as pancytopenia and combined degeneration of the spinal cord. Patients with neurological symptoms may exhibit no haematological abnormalities, and vice-versa. However, if treatment is delayed, irreversible neurological damage may occur[1]. Therefore, an early vitamin B12 deficiency diagnosis is essential for prompt, appropriate treatment.

In 1951, Conley and Krevans[2] proposed a possible interaction between low levels of vitamin B12 and high levels of folate based on a worsening of neurological symptoms in patients with pernicious anaemia treated with high doses of folic acid. In 2022, Selhub et al.[3] hypothesised the specific aetiology of this interaction. The excessive intake of folic acid depletes the vitamin B12-transcobalamin complex, decreasing active vitamin B12 in the circulation and limiting its availability for tissues. In addition, a number of studies have also reported a higher prevalence of cognitive impairment in individuals with vitamin B12 deficiency and high serum folate concentrations[4-5].

This study reports the case of a patient who presented to the emergency department with balance disorders and a blood count indicating macrocytosis. Vitamin B12 deficiency and high folate value were also detected in the patient.

CASE DESCRIPTION

A 56-year-old female patient presented to the emergency department of the Sandro Pertini Hospital (Rome, Italy) in May 2023 with progressive gait disturbance, muscle weakness and leg numbness in the previous five months. The patient had a previous history of hypertension, two spontaneous abortions and quadrantectomy for breast cancer in 2011 (histological examination was not provided to us). At-home drug therapy included a β-blocker (bisoprolol fumarate 2.5 mg per day) and olmesartan medoxomil 20 mg per day for arterial hypertension, fluoxetine (20 mg per day) for depression, and acetylsalicylic acid (100 mg per day) and folic acid (5 mg per day, as the formulation on sale in Italy). These were prescribed when the patient was 26 years old following the spontaneous abortions, and the patient had taken them on an almost regular basis over the past 30 years. The patient was unable to specify the reason for the prescription. In addition, the patient followed a vegan diet. The last blood tests had been conducted in 2019 for a check-up, but no abnormalities were noted, according to the patient.

The patient was well-oriented without cognitive dysfunction using the Montreal Cognitive Assessment, had 4/4 muscle strength in the limbs based on the Medical Research Council scale, was only able to assume a standing position with an enlarged base, was Romberg positive and had a markedly ataxic gait. A blood test revealed macrocytosis with a mean corpuscular volume of 103 f/l (normal range 82–98 f/l), and the brain computed tomography result was negative. At this stage, the patient was hospitalised for further diagnostic tests. Somatosensory evoked potentials detected an increase in latency from the baseline in the left tibial nerve and no signal was induced in the right tibial nerve. The electromyography and electroencephalogram test results were within the normal limits. In addition, brain and spinal cord magnetic resonance imaging (MRI) with contrast agent did not reveal significant abnormalities *(Fig. 1)*. For the finding of macrocytosis we measured the vitamin B12 level and folate level: the vitamin B12 level was 84 pg/ml (normal range 197–771 pg/ml) and the folate level was >24 ng/ml (normal range 2.5–20 ng/ml). At this stage, the patient began B12 therapy (cyanocobalamin 1 mg by intramuscular injection twice a week), the folate therapy was discontinued, and the fluoxetine dose was increased from 20 to 40 mg per day.

An oesophagogastroduodenoscopy was performed next to detect signs of atrophic gastritis or celiac disease. The macroscopic appearance was normal, but a bioptic examination revealed *Helicobacter pylori* (HP) fundal, not atrophic gastritis, and an increased number of intraepithelial CD3 lymphocytes (>25 intraepithelial lymphocytes IELs/100 enterocytes) in the duodenum, diagnosed as a grade A coeliac lesion according to the Corazza-Villanacci classification.

Further blood tests revealed that anti-mitochondrial antibodies, anti-smooth muscle antibodies, anti-liver-kidney microsomal antibodies, anti-parietal cell antibodies,

anti-gliadin IgG and IgM, anti-transglutaminase IgA, anti-cardiolipin antibodies, homocysteine, CA 19.9, CA 125, CA 15.3 and α-fetoprotein were all negative. Anti-nuclear antibodies were positive (1/80 IFI Hep-2) (normal value absent 1:80). In addition, carcinoembryonic antigen was 3.1 U/ml (normal range 0–2.5 U/ml).

A rectosigmoid colonoscopy was then performed to study the last ileal loop. Only a 2 cm sessile polyp was detected at 5 cm from the anal margin. Histologic examination revealed tubular villous adenoma with low-grade dysplasia according to the World Health Organization guidelines.

After nine days of therapy the patient showed a general improvement of the symptoms and was therefore re-evaluated by the neurologist. The evaluation indicated an improvement in the gait disturbance. Specifically, the gait appeared more autonomous, even if cautious, with a slightly enlarged base and minimal Romberg's oscillations. There were also notable improvements in paraesthesia in the lower limbs. The patient was discharged after 10 days of hospitalisation with indications for supplementary therapy of B12 and remote outpatient re-evaluation.

The final diagnosis was as follows: i) vitamin B12 deficiency; ii) combined degeneration of the spinal cord; iii) tubular villous adenoma with low-grade dysplasia according to WHO; iv) autoimmune diathesis; and v) grade A coeliac lesion according to the Corazza-Villanacci classification.

During the hospital stay the patient began B12 therapy (cyanocobalamin 1 mg by intramuscular injection twice a week) and the folic therapy was discontinued because of the high folate value. After 10 days the patient was discharged from the emergency department and admitted to a rehabilitation unit. Monthly intramuscular injections of cyanocobalamin 5 mg were continued for 2 months. Following treatment with cyanocobalamin, the vitamin B12 level was determined to be in the upper reference range (890 pg/ml) and the patient showed clinical improvement. Specifically, ambulation was restored. The patient then left the rehabilitation unit.



Figure 1. Brain and cervical spine magnetic resonance imaging: sagittal T2/FLAIR images without signal changes.

DISCUSSION

Vitamin B12 is contained within foods of animal origin, and in Western countries the average daily intake with the common diet is ~ 5–30 µg, of which only 1–5 µg is absorbed. In the acidic stomach, ingested vitamin B12 binds to haptocorrin, from which it is detached in the duodenum by pancreatic enzymes before binding to intrinsic factor. The vitamin B12-intrinsic factor complex passes through the enterocytes of the ileum where it is broken down, following which vitamin B12 is finally transported to the tissues by transcobalamin. Therefore, vitamin B12 deficiency has a number of potential causes involving each of these steps, such as inadequate diet or reduced absorption (due to autoimmune metaplastic atrophic gastritis or other forms of gastric mucosal destruction, gastric resection or bypass). Other causes may be inhibition of intrinsic factor, hypochlorhydria and pancreatic pathologies that interfere with binding, reduction of the ileal absorption surface (such as in inflammatory bowel disease or coeliac disease), consumption by intestinal bacteria or parasites, and genetic mutations.

Cases of vitamin B12 deficiency and autoimmune diseases (such as Sjögren's syndrome, pharyngeal-cervical-brachial Guillain-Barré syndrome, autoimmune thyroiditis, autoimmune gastritis, rheumatoid arthritis, ulcerative colitis) have been reported and in some cases vitamin B12 deficiency appeared to be a result rather than a cause of the syndrome[6-7]. In the present case study, only anti-nuclear antibodies were positive in the blood test results, suggesting an immune disease diathesis; however, no other confirmatory data were obtained. Furthermore, the esophagogastroduodenoscopy biopsy exam revealed HP-fundal not atrophic gastritis and an increased number of duodenal intraepithelial CD3 lymphocytes (>25 IELs/100 ECs), indicating a A grade coeliac lesion, according to the Corazza-Villanacci classification. However, the anti-transglutaminase and antigliadin antibodies were negative, excluding the diagnosis of celiac disease.

Previously, cases in which high doses of oral folic acid worsened the neurological symptoms of patients with pernicious anaemia have been reported. This is in addition to instances where a high prevalence of anaemia and cognitive impairment were found in patients with vitamin B12 deficiency and high serum folate levels[4-5]. Selhub et al. have also described the biochemical interaction between vitamin B12 and folate[3]. Specifically, an excessive oral intake of folic acid leads to a reduction in the active fraction of vitamin B12, holotranscobalamin, and this decrease exacerbates the deficiency itself. It should be noted that the recommended daily dose of folic acid is 0.4 mg and therefore the intake of folic supplements or fortified foods in the diet is sufficient to cause vitamin B12 deficiency. The patient described in

this study had been taking ~5 mg of folic acid per day for 30 years and her serum folate value was >24 ng/ml. We therefore hypothesise that the high-folate-low-vitamin B12 interaction represents the cause of vitamin B12 depletion in this patient.

The neurological signs and symptoms of vitamin B12 deficiency are due to demyelination of the posterior and lateral columns of the spinal cord, termed subacute combined degeneration (SCD). The pathophysiological underlying cause of this typical localisation has not yet, to the best of our knowledge, been clarified. However, SCD with an initially normal level of vitamin B12 has been reported[8] and in a study by Linazi et al.[9] only 8 out of 42 patients diagnosed with subacute combined degeneration showed typical abnormalities on an MRI scan. It was suggested that adynamia is a marker for SCD as it was the only marker found in all patients[8]. In this study, a brain white matter abnormality was found from an MRI of the patient, but not abnormally high signals at the spinal cord.

CONCLUSIONS

We propose that all patients with neurological signs and symptoms should be tested for possible vitamin B12 deficiency, since early diagnosis and treatment could stop the progression of the disease and allow the regression of the neurological deficit before it becomes irreversible. It is important not to rely on blood count values to diagnose a vitamin B12 deficiency as the neurological and haematological outlook may be inversely proportional. As demonstrated in a meta-analysis by Alruwaili et al.[10], it is necessary to provide appropriate dietary counselling in all individuals at risk of vitamin B12 deficiency to prevent neurological deficits. At present, the duration of vitamin B12 supplementation has not been definitively established.

To the best of our knowledge, this study is the first to report a case from Italy of combined sclerosis and high-folate-low-vitamin B12 interaction; it is therefore of interest to public health decision makers and clinical practice.

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