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Unusual association of diseases/symptoms

Multiple sclerosis-like neurological manifestations in a coeliac patient: nothing is as it seems

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Summary

Cobalamin (vitamin B_{12}) deficiency occurs with several disorders, involving different organs and systems, including blood, bowel, nervous system and eyes. Although the most important features are usually haematological ones, presence of neurological involvement, in the absence of blood count alterations, has just been described in the literature. Here we report the case of a 48-year-old man, suffering from coeliac disease for approximately 5 years, vegetarian, who was admitted to our department, referring dysaesthesia of the left lower limb, decreased libido and erectile dysfunction. Vitamin B_{12} deficiency was proved, even in the absence of blood count alteration, and treated with a vitamin supplement, resulting in complete remission.

BACKGROUND

A severe cobalamin (Cbl, vitamin B_{12}) deficiency can occur with several disorders, involving different organs and systems, including blood, bowel, nervous system and eyes.[1–4] Although most of the patients have predominant haematological manifestations, the presence of neurological involvement, in the absence of blood count alterations, has already been described. Moreover, a folic acid supplement increases the risk of purely neurological presentation, because it masks the haematological effects of vitamin B_{12} deficiency. First neurological onset is represented by numbness and limb 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] Neurological disorders completely regress after Cbl administration.[12 13]

In this report, we describe the case of a vegetarian man aged 48, suffering from coeliac disease, under a gluten-free diet, affected with hypovitaminosis B_{12}-related multiple sclerosis-like neurological manifestations, in the absence of haematological disorders and/or other symptoms or signs of organ distress. We excluded the hypothesis of a lack of strict adherence to the gluten-free diet and of malabsorption due to 'active' coeliac disease, as antitransglutaminase and antiendomysial antibody assays were all negative during the follow-up examinations, and duodenal histology showed normal duodenal villi length (ie, Marsh 1 degree). Consequently, the primary cause of hypovitaminosis B_{12} and neurological symptoms was likely an intake deficiency through food. Moreover, the intake of vegetable foods, with high folate contents, may have led to the absence of detectable haematological abnormalities.

CASE PRESENTATION

A 48-year-old man, who had suffered from coeliac disease for approximately 5 years and was following a gluten-free diet, was admitted to our department in February 2006, referring dysaesthesia, starting from the left inguinal region and spanning the entire ipsilateral lower limb, for about 7 months, followed after 5 months by decreased libido and erectile dysfunction.

In November 2000, due to a family history of coeliac disease (brother and nephew) that was, however, asymptomatic without symptoms/signs attributable to malabsorption disorders, the patient underwent antitransglutaminase IgG and IgA (positive) and antiendomysial IgA (positive at a titre of 1 : 320) antibody assays and human leucocyte antigen typing (DQ2 positive). Upper gastrointestinal tract endoscopy showed 'a small sliding hiatal hernia; discoloration of the antral mucosa; normal bulb and second portion of the duodenal mucosa', while duodenal biopsy found 'marked villous atrophy and severe inflammation of the lamina propria (Marsh 3c)', thus confirming the coeliac disease diagnosis. The patient therefore started a gluten-free diet and was periodically (yearly) followed up as an outpatient. After 1 year of the gluten-free diet, his general clinical condition was good, there were no abnormalities on physical examination, and routine blood chemistry tests were normal, except for slightly increased transaminases (×1.5 the normal value), hyposideraemia (12 mg/dl, male reference range 59.0–158.0 µg/dl) and hypoferritinaemia (4 ng/ml, male reference range 30.0–400.0 ng/ml). Serum antiendomysial IgA antibody assay was negative due to strict adherence to the gluten-free diet.

In July 2005, he reported the onset of numbness, described as a 'pulse-vibration' extending from the left groin to the entire ipsilateral lower limb, followed in

December of the same year by decreased libido and erectile dysfunction. Physical examination was unrewarding, but neurological examination showed tendon reflex asymmetry, which was more evident on the right. Consequent brain MRI with intravenous contrast showed 'hyperintense multiple periventricular and subcortical lesions' (figure 1), and a full spine MRI with intravenous contrast detected 'hyperintensity at D9–D10 levels and disc protrusions at L3–L4 and L4–L5'. The above findings suggested a diagnosis of 'demyelinating leukoencephalopathy'.

In January 2006, the following were performed: cytomegalovirus (CMV) IgM and IgG antibody ELISA, CMV IgG avidity and HIV ELISA evaluation, all with negative results. Other autoantibody assays (antinuclear antibodies, antimitochondrial antibodies, antismooth muscle antibodies, liver/kidney microsomal antibodies, antiactin antibodies, antiparietal cell antibodies and antiglomerular basement membrane antibodies) were also negative, with the exception of antinuclear antibodies, which were positive at a titre of 1 : 80.

In February 2006, the patient requested a consultation at the specialist 'Centre for Studies of Multiple Sclerosis', where routine blood tests were performed, all of which were within the normal ranges, except for hypovitaminosis B_{12} (51 pmol/l, reference range 156–672 pmol/l) and hypercholesterolaemia (twofold the normal value). Tests were also performed to evaluate serum folate (within the reference range), viral B and C hepatitis markers (negative), lupus anticoagulant (absent), serum complement factors C3 and C4 (within the reference range), free T3, free T4 and thyroid-stimulating hormone (within the reference range) and homocysteinaemia (within the reference range). Moreover, the patient underwent EEG, acoustic, visual and somatosensory-evoked potentials and cerebrospinal fluid examination, which were all within normal limits. Since the cerebrospinal fluid data were negative, which did not support the demyelinating leukoencephalopathy diagnosis, the diagnosis was changed to 'multifocal leukoencephalopathy under clinical surveillance, in a patient with celiac disease, hypovitaminosis B_{12} and dyslipidemia'. Low-dose oral vitamin B_{12} treatment was recommended, as well as follow-up brain and spinal cord MRI with contrast, and after 6 months echo colour Doppler imaging of the carotid vessels and a gastroenterological examination.

The same month the patient was readmitted to our outpatient clinic for oesophag-gastroduodenoscopy with gastric and duodenal biopsies (hiatal hernia, chronic atrophic gastritis and Marsh 1 at D2 were observed). An accurate anamnesis of the patient's dietary habits revealed that he had been a vegetarian for 10 years. High-dose intramuscular vitamin B_1, B_6 and B_{12} complex therapy was prescribed three times a week. Moreover, he underwent antiparietal cell and intrinsic factor antibody assay (negative), carotid Doppler ultrasound (no pathological abnormalities) and sacral somatosensory-evoked potentials test (abnormal due to a pathological latency increase in P40 values).

Approximately 1 week after the administration of four doses of intramuscular vitamins B_1, B_6 and B_{12} complex the patient reported the disappearance of dysaesthesia, recovery of libido and normalisation of erectile function. Accordingly, we confirmed the treatment and also added folic acid (15 mg/day per os). Twenty days later, after 11 doses of intramuscular vitamins B_1, B_6 and B_{12} complex had been administered, the therapy was changed, reducing intramuscular vitamins B_1, B_6 and B_{12} complex to 1 phial/week and folic acid to 15 mg/2 days a week. Serum vitamin B_{12} was assayed after 45 days of treatment, showing values >1200 pg/ml (normal range 174–878 pg/ml), as well as serum folate, which was within the normal reference range.

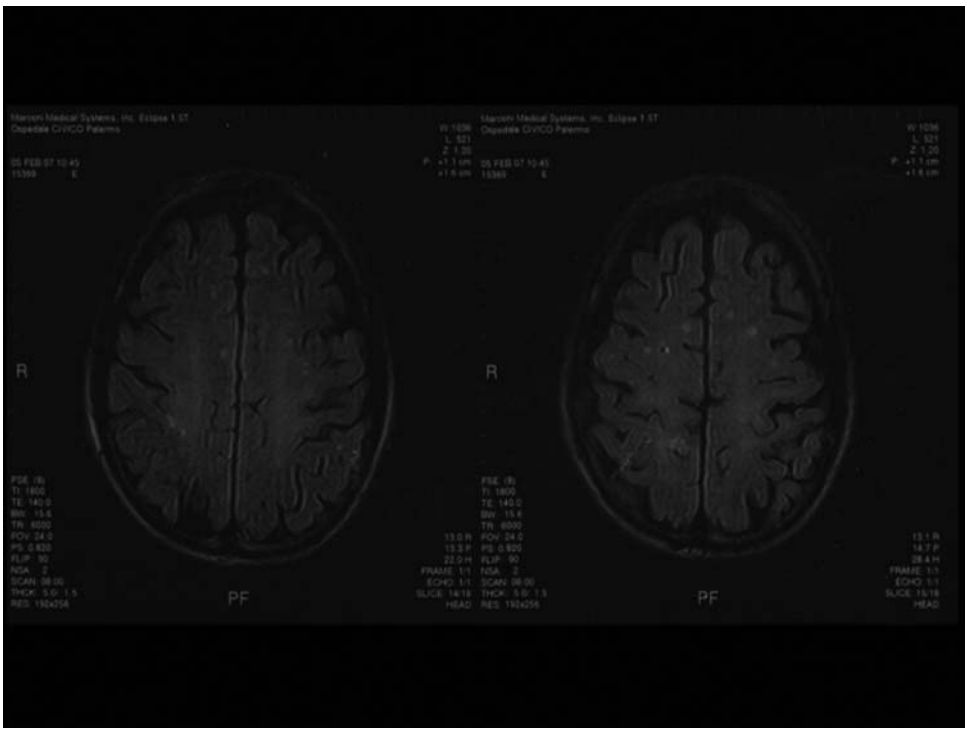

Figure 1 Brain MRI with intravenous contrast, showing multiple periventricular and subcortical hyperintense lesions.

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OUTCOME AND FOLLOW-UP

The patient is still being followed up as an outpatient in our department due to the continued vitamin supplement treatment to evaluate vitamin B_{12} and folate serological values and investigate occasional reported dysaesthetic disturbances. Brain and spinal cord MRI with intravenous contrast performed after 12 months of therapy showed 'improvement of hyperintense periventricular and subcortical lesions and disc protrusions at L3–L4 and L4–L5'. Antitransglutaminase and antiendomysial antibody assay remain negative.

DISCUSSION

In this report we described the case of a vegetarian man, aged 48, suffering from coeliac disease on a gluten-free diet, with hypovitaminosis B_{12}-related multiple sclerosis-like neurological manifestations, in the absence of haematological disorders and/or other symptoms or signs of organ distress.

The correct approach to hypovitaminosis B_{12}-related neurological presentation includes accurate identification of the anatomical site of injury in order to reduce the aetiology list. Dysaesthesia, decreased libido and erectile dysfunction, the presenting symptoms in our report, may be the result of damage to the parietal cortex, deep white matter, thalamus, brain stem, spinal cord, spinal nerves or peripheral nerves. Brain and spinal cord MRI with intravenous contrast identified the lesions as 'multifocal leukoencephalopathy' or 'white matter disease'. The latter is classified according to histopathological criteria as *demyelinating* (characterised by the loss of normal myelin, by an autoimmune/inflammatory process ie, multiple sclerosis), *dysmyelinating* (usually metabolic, centred on the unusual nature of myelin content, ie, metachromatic leukodystrophy), *hypomyelinating* (marked by a reduced production of myelin, ie, Pelizaeus-Merzbacher disease) and *myelinolytic* or *spongiform* (associated with myelin cystic degeneration, ie, central pontine myelinolysis). Pathogenic considerations have also been added to the histopathological classification; thus at present it must be reclassified as 'acquired' or 'hereditary' (also known as 'leukodystrophy') white matter diseases. The main aetiological factors responsible for the above-mentioned histopathological abnormalities are reported in table 1.[14–16]

In our case, after excluding a primary hypothesis of multiple sclerosis demyelinating multifocal leukoencephalopathy based on the negative cerebrospinal fluid examination and finding severe hypovitaminosis B_{12}, a vitamin deficiency was considered a likely origin for the neural abnormalities. Although in many patients with vitamin B_{12} or Cbl deficiency haematological manifestations are predominant, they are variously associated with gastroenterological, neurological and psychiatric ones. The present purely clinical neurological presentation, with no detectable abnormalities in blood cell count, has already been described in the literature. In this respect, it should be pointed out how a folate supplement can mask the haematological effects of vitamin B_{12} deficiency (ie, megaloblastic anaemia), as was the case in our long-term vegetarian patient, increasing the risk of neural damage and resulting neurological disorders.[17 18]

The first neurological findings are numbness and tingling in the limbs, 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. There are possible although rare signs of cerebellum dysfunction, peripheral neuropathy, sphincter disturbances, optic atrophy and orthostatic hypotension.[5–11]

Daily minimum vitamin B_{12} requirement is 2.5 μg/day, the only source being animal products. The body stores 3–5 mg, mainly in the liver; therefore clinical signs of vitamin introduction deficiency or malabsorption only appear after a period ranging from 2 to 5 years.[1–4 19–21] The most important causes of vitamin B_{12} deficiency are listed in table 2.[22]

To date, the pathogenesis of neurological disorders in patients with Cbl deficiency has not been clarified. Some authors argue that neurological damage can be attributed, at least in part, to deficiency in methionine synthesis, with effects on myelin fatty acid synthesis. A new hypothesis considers the abnormal Cbl deficiency-induced synthesis of certain cytokines (ie, tumour necrosis factor and interleukin-6), which has been proven to have a lytic effect on myelin.[19–23]

Although Cbl deficiency can present primarily with a degeneration of the posterior and lateral cords of the spinal cord, thus causing symptoms/signs of peripheral neuropathy, there is a possible although rare involvement of the peripheral nerves and cerebral cortex and, more rarely still, cerebellar cortex. In the early stages, the

Table 1 Pathophysiological classification of white matter disease

I. Non-infectious inflammatory disorders
Multiple sclerosis and its variants
Acute disseminated encephalomyelitis
II. Infectious-inflammatory disorders
Congenital CMV infection
CMV subacute encephalitis
HIV subacute encephalitis
Subacute sclerosing panencephalitis
Progressive multifocal leukoencephalitis
Other infections
III. Toxic–metabolic disorders
Central pontine and extrapontine myelinolysis
Vitamin B_{12} deficiency
Folate deficiency
Marchiafava-Bignami disease
Malnutrition
Toxic encephalopathies (endogenous–exogenous)
IV. Hypoxic–ischaemic disorders
Cerebral autosomal dominant arteriopathy with subcortical infarcts and Leukoencephalopathy
Periventricular leukomalacia
Polycystic leukoencephalopathy
Delayed hypoxic–ischaemic demyelination
Subcortical arteriosclerotic encephalopathy (Biswanger disease)
Normal ageing
Vasculitis (in the course of systemic lupus erythematosus, Bechet's disease, etc)
Radiations
V. Traumatic disorders
Shearing
Oedema

CMV, cytomegalovirus

Table 2 Stages of cobalamin metabolism and corresponding causes of cobalamin deficiency

Stages and actors in cobalamin metabolism	Causes of cobalamin deficiency
1. Intake solely through food	• Strict vegetarianism ('vegans' or patients who are sick in institutions or in psychiatric hospitals)
2. Digestion brings into play	
• Gastric secretions (hydrochloric acid and pepsin) • Haptocorrin • Intrinsic factor • Pancreatic and biliary secretions • Enterohepatic cycle	• Gastric achlorhydria • Gastric secretion blocking drugs • Gastrectomies (partial or total) • Pernicious anaemia • Intrinsic factor congenital absence or malfunction (rare)
3. Absorption brings into play	
• Cobalamin-intrinsic factor complex • Terminal ileum • Cubilin and amnionless (Cubam receptor) • Calcium and energy	• Diseases of the terminal ileum - Tropical sprue - Non-tropical sprue - Regional enteritis - Granulomatous disorders (rare) - Malignancies • Competition for cobalamin - Parasitism (ie, tapeworms) - Small intestinal bacterial overgrowth • Ileal or small bowel resections • Imerslund-Grasbeck syndrome (rare)
4. Transport by transcobalamins	• Congenital deficiency in transcobalamin II
5. Intracellular metabolism based on various intracellular enzymes	• Nitrous oxide anaesthesia • Congenital deficiency in various intracellular enzymes

Dali-Youcef and Andres[22] (modified).

histological framework consists of demyelinating lesions visible as multiple hyperintense areas on T2-MRI. These are followed by axonal degeneration and finally by irreversible neuronal death. The earliest neurological manifestations are numbness and tingling in the limbs, followed by progressive spastic paresis and ataxia. Pulse, position and kinetic sensitivity are generally reduced, Babinsky and Romberg signs can be positive and evoked potentials are often abnormal. Signs of cerebellar dysfunction, peripheral neuropathy, sphincter disturbances, optic atrophy and orthostatic hypotension are possible, although rare.[5–11]

In our case, the rapid disappearance of neurological symptoms following treatment with a vitamin B_{12} supplement confirmed the hypothesis of 'deficiency leukoencephalopathy'. The mainstay of vitamin B_{12} deficiency treatment is replacement, preferably via parenteral administration, as the deficiency is generally linked to a defect in absorption. The dosage should correspond to the vitamin B_{12} levels and clinical manifestations of the patient, the initial parenteral treatment usually being 1000 μg of Cbl for 8 weeks, followed by 1000 μg of Cbl per month for life. The response is usually satisfactory, with the resolution of haematological disorders and disappearance or relief of neurological symptoms, although these symptoms are not always reversible.[12 13] However, the patient had a chronic atrophic gastritis, histologically proven. In conjunction with vitamin B_{12} deficiency, this is at least highly suspicious of pernicious anaemia. Negative antibodies against parietal cells and intrinsic factor could exclude the diagnosis, but sensitivities of 27% and 81%, respectively, have been described.[24–26] In addition, coeliac disease is known to be associated with other autoimmune diseases. Furthermore, the patient had been prescribed oral vitamin B_{12} treatment (without success), but rapidly improved after intramuscular supplementation—a typical feature. Thus, we cannot entirely exclude the diagnosis of pernicious anaemia, although negative specific autoantibodies make this diagnosis less likely. Moreover, it is also possible to hypothesise that patient chronic atrophic gastritis might be related to a *Helicobacter pylori* infection, unfortunately not investigated. In our patient we also excluded the hypothesis of a lack of strict adherence to the gluten-free diet, as antitransglutaminase and antiendomysial antibody assays were all negative during the follow-up examinations after 2004. Finally, duodenal histology was re-evaluated at the onset of the neurological symptoms, as it has been demonstrated that villous atrophy can persist several years after commencement of a gluten-free diet, despite strict adherence to the diet.[27] However, the patient showed normal duodenal villi length (ie, Marsh 1 degree), thus excluding malabsorption due to 'active' coeliac disease. Consequently, the primary cause of hypovitaminosis was likely an intake deficiency through food.[28 29] Moreover, the intake of vegetable foods, with high folate contents, may have led to the absence of detectable haematological abnormalities.[18]

Learning points

- Cobalamin (vitamin B_{12}) deficiency occurs with several disorders, involving different organs and systems, including blood, bowel, nervous system and eyes.
- Although the most important features are usually haematological ones, the presence of neurological involvement (ie, multiple sclerosis-like neurological manifestations), in the absence of blood count alterations, has recently been described in the literature.
- In our patient—examined for multiple sclerosis-like neurological manifestations, vegetarian, with a documented hypovitaminosis B_{12} and also affected with coeliac disease—we excluded the hypothesis of a lack of strict adherence to the gluten-free diet and of malabsorption due to 'active' coeliac disease.
- Consequently, the primary cause of hypovitaminosis B_{12} and neurological symptoms was likely an intake through food deficiency. Moreover, the intake of vegetable foods, with high folate contents, may have led to the absence of detectable haematological abnormalities.
- The patient was successfully treated with parenteral administration of a vitamin B_{12} supplement.

Competing interests None.

Patient consent Obtained.

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