The neuropsychiatric manifestation of vitamin B12 deficiency: Two case reports and literature review

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ABSTRACT Vitamin B12 deficiency is a common condition that manifests classically with megaloblastic anaemia. However, neuropsychiatric disorders can occur as the first manifestation of vitamin B12 deficiency. Herein, we reported two cases with neuropsychiatric disorders as the first manifestation. The first was an Indian man who presented with an unsteady gait and numbness in the lower limbs associated with low back pain and normal haemoglobin with normocytosis. MR images were consistent with subacute combined degeneration of the spinal cord. Vitamin B12 level was found to be low. The second case was an Indian man without a psychiatric history who was brought to the emergency room because of abnormal behaviour and poor sleep. His blood study and brain images were normal. The deterioration of his condition in addition to being vegetarian prompted the attending physician to look for another cause of his illness. Vitamin B12 was low. Both patients received B12 supplements and showed significant improvement.

KEYWORDS subacute combined degeneration, vitamin B12 deficiency, macrocytosis, catatonia

Introduction

Vitamin B12 (B12) is an essential nutrient necessary for the proper function of the nervous system and erythropoiesis. Therefore, any deficiency of this nutrient can cause megaloblastic anaemia and a wide variety of neuropsychiatric disorders. [1] There are various causes of B12 deficiency including poor intake (i.e., vegetarianism), malabsorption of vitamin B 12 (i.e., lack of intrinsic factor and malabsorption of protein-bound B12), general malabsorption (i.e., celiac disease, bacterial growth notably Helicobacter pylori) and competition for B12 (i.e., nitrous oxide poisoning or metformin therapy). [1-3] In one case series, the leading causes of B12 deficiency were poor intake and malabsorption of B12 (i.e., intrinsic factor deficiency). [1] Vegetarians and elderly are at high risk for B12 deficiency, due to abstaining from the consumption of animal products in the first group and age-related gastric atrophy in the second group. In this report, we presented two cases of B12 deficiency associated with neuropsychiatric disorders; the first one presented as subacute combined degeneration of the spinal cord, while the other was presented as catatonia. These two cases highlight the importance of considering B12 deficiency in the differential diagnosis of neuropsychiatric disorders that lack a clear aetiology or in vegetarians.

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Case presentations

Case 1

A 48-year-old Indian man presented to our hospital with an unsteady gait and numbness in the lower limbs associated with low back pain over the past 15 days. His medical and social history was unremarkable. He consumed a balanced diet and denied drinking alcohol. On examination, the patient was conscious well oriented with stable vitals. Neurological examination showed ataxic gait and positive Romberg sign. Vibration and position senses were absent over the lower extremities. The rest of his examination was normal.

Investigations showed a haemoglobin of 13.3 g/dl (with normal mean corpuscular volume), white blood cell of 7500/µL and platelets of 229000/ µL. Blood chemistry, thyroid function test and lipid profile were within normal limits. HIV and syphilis serology tests were negative. Copper and ceruloplasmin levels were normal as well as serum folate. Serum B12 level was 63 pmol/l (N: 133–675 pmol/l), and serum homocysteine level was

133 µmol/L (N: 4-12 µmol/L).

Computed tomography of the brain was mostly normal. MRI showed evidence of diffuse intramedullary increased T2 signal intensity seen affecting the dorsal aspect of the spinal cord, extending from lower cervical cord down to involve the rest of the cord. The post intravenous contrast MR images showed areas of enhancement could be demonstrated within the spinal cord, corresponding to the abnormal signal intensity areas on T2.

Given these findings, the patient was diagnosed with subacute combined degeneration (SCD) of the spinal cord due to vitamin B12 deficiency. Anti-parietal antibody test and Intrinsic factor antibody test were positive. Upper gastrointestinal endoscopy was performed, and gastric and duodenal biopsies were obtained. Histological studies showed mild chronic gastritis, no intestinal metaplasia, dysplasia or malignancy. Test for H. pylori was negative.

The patient was admitted to our hospital as a case of subacute combined degeneration of the spinal cord due to pernicious anaemia. B12 (cyanocobalamin) intramuscular injections (1000 µg/day) and physiotherapy were initiated. One week after being hospitalized, he was discharged to continue with B12 once a week for four weeks, then once a month for one year, then once a year for the rest of his life. Two months later, the patient was seen in the clinic without numbness and with an almost normal gait. After one year, the patient was seen in the clinic; he was completely normal with a B12 level of 340 pmol/l and repeat MRI showed complete resolution of the previous brain lesions.

Case 2

His uncle brought a 31-year-old Indian man without a psychiatric history to the emergency department because of abnormal behaviour and poor sleep over the past ten days. The history was obtained from his uncle who stated that he observed that his nephew had not slept well for the past ten days and used to sit alone and did not interact with his roommate or uncle. He was a vegetarian but has denied drinking alcohol. His medical history was unremarkable. He was engaged and about to get married the following month. He was a carpenter but had been unemployed for the last two weeks.

On examination, the patient was conscious, oriented to time, persons and places. He was calm and talking coherently. Vitals were stable, and examination of cardiovascular, respiratory and neurological systems was normal.

A psychiatric consultation was requested, and the patient was examined by a psychiatrist and was diagnosed with an adjustment disorder. The patient began with olanzapine 10 mg daily at bedtime and promethazine with 50 mg intramuscularly administered once and was discharged home to be seen at the clinic. After one week, he was brought to psychiatry clinic due to worsening of his condition. On examination, he was mute, and the psychiatrist noted that when he placed the patients' arms in uncomfortable positions, he maintained the postures unless changed by him. This finding was consistent with catatonia. No investigations or brain imaging had been performed. He was admitted to psychiatry hospital and started on haloperidol 5mg intramuscular once daily and promethazine 50 mg intramuscular twice daily. Haloperidol was replaced by diazepam on the next day. Ten days after being admitted, the patient developed stiffness on both arms (waxy flexibility, catatonia), but he was talking coherently and to the point. The speech rate, volume and tone were normal, and there was no pressure speech. Investigations showed high CK (2716 u/l), high homocysteine and low serum B12 level (73.7 pmol/l), while the thyroid function test and serum folate were normal. Haemoglobin was 14000/μL, and the MCV was 98 fl, while white blood cells and platelets were adequate.

Blood chemistry was within normal limit. The patient was transferred to Hamad general hospital and was admitted in the medical ward. On admission, the patient was mute with hand held in the air with waxy flexibility. Other examinations were normal. Brain CT and Brain MRI were unremarkable. An intramuscular injection of vitamin B12 (cyanocobalamin) was started at a dose of 1000 μg / day and lorazepam tablets 2 mg every 8 hours. On the third day of admission, he improved and psychosis resolved. He was discharged to follow psychiatric clinic as well as haematology clinic.

Discussion

The clinical presentation of B12 deficiency widely varies; it includes macrocytic anaemia, which usually occurs early, gastrointestinal manifestations and neuropsychiatric symptoms such as neuropathy, myelopathy, depression, catatonia and dementia. [1-4] Neuropsychiatric disorders as the first manifestation without related anaemia or macrocytosis are uncommon and represent a diagnostic dilemma. As noted in case 1, the patient presented with unsteady gait with numbness in the lower limbs and lower backache, while the examination revealed positive Romberg sign and absence vibration/position senses in the lower extremities. The differential of these findings includes nutritional aetiology (Copper, B12 and vitamin E deficiency), paraneoplastic disorder, autoimmune myelopathy, multiple sclerosis, Friedreich's ataxia, Adult-onset autosomal-dominant leukodystrophy with autonomic symptoms and HIV related myelopathy. [5] Vitamin B12 deficiency was missed initially as there was no anaemia or macrocytosis and many unnecessary investigations were requested before asking for spinal MRI, which was very helpful in guiding us to the diagnosis. On the other hand, our second patient who was previously healthy presented with abnormal behaviour and sleep deprivation. Vitamin B12 deficiency was overlooked, which is consistent with previous reports from India, [6], and the patient was initially diagnosed with an adjustment disorder and given olanzapine and promethazine, but without benefit. The deterioration of his condition in addition to being vegetarian prompted the attending physician to look for another cause of his illness. As a consequence one must agree that B12 deficiency as a cause of neuropsychiatric disorders may be overlooked by the physicians, leading to unnecessary investigations, inadequate treatment and delayed diagnosis.

The exact mechanism of SCD of the spinal cord is not fully understood. One of the proposed mechanisms suggests that vitamin B12 deficiency results in defective myelin synthesis in two ways. Firstly, B12 deficiency leads to reduced S-adenosylcobalamin, which is required for the conversion of methylmalonyl coenzyme A (CoA) to succinyl-CoA, increasing the serum methylmalonic acid (MMA) that decreases myelin synthesis along with the incorporation of abnormal fatty acids into neuronal lipids. Secondly, B12 deficiency leads to the accumulation of intracellular and serum homocysteine, which has potentially toxic effects on neurons and vascular endothelium. Consequently, axonal demyelination, degeneration and later death will occur as a hallmark of vitamin B12 deficiency induced neuronal damage resulting in peripheral or autonomic neuropathy, SCD of the spinal cord, delirium and dementia. [7] Another proposed mechanism derived from rat models, suggests that B12

deficiency in the gastrectomized rat model, leads to increased spinal cord synthesis and increased cerebrospinal fluid (CSF) levels of neurotoxic factors such as tumor necrosis factor-alpha (TNF-α) and nerve growth factor (NGF), while at the same time, B12 deficiency decreases spinal cord synthesis and CSF levels of neurotrophic factors such as interleukin 6 (IL-6), and epidermal growth factor (EGF). The net effect of these events may lead to neuropsychiatric manifestations that accompany vitamin B12 deficiency. [8] Generally, the diagnosis is usually based on identifying a low serum B12 level with clinical evidence of deficiency, which response to replacement therapy. If the B12 level is borderline or normal, but the clinical suspicion of deficiency still exists, elevated levels of the metabolites such as homocysteine and methylmalonic acid can help to establish the diagnosis. [9-11] There is no consensus on vitamin B12 deficiency screening because the clinical severity of vitamin B12 deficiency is not related to vitamin B12 levels. Moreover, the lack of another reliable diagnostic tool or a standard gold test makes screening challenging to perform. [9,10] Both of our patients had low serum B12 and high homocysteine levels. After confirming the diagnosis, looking for the underlying cases is mandatory, as the treatment line depends on the aetiology. Indications to initiate cobalamin therapy include well documented megaloblastic anaemia or other haematological abnormalities or neuro-psychopathy. [10]

Treatment with vitamin B12 supplements prevents further subacute combined degeneration of spinal cord by three different mechanisms; it converts homocysteine to methionine, increases the conversion of methylmalonyl coenzyme A (CoA) to succinyl-CoA, and reduces spinal cord synthesis and CSF levels of neurotoxic factors. Moreover, B12 supplement rejuvenates the damaged neurons by increasing the production of myelin resulting in partial to full recovery of existing SCD lesions depending on the duration and extent of neurodegeneration. [12] In treating neuropsychiatric disorder due to cobalamin deficiency, the clinical response is inversely proportional to the magnitude and duration of the disease. Recovery may be complete if symptoms have only been present for a few weeks before the start of treatment. [13] Cases 1 and 2, received their treatment promptly after diagnosis, and therefore showed excellent response to vitamin B12 supplementation.

In conclusion, these two cases demonstrated that B12 deficiency could be overlooked at the beginning due to highly variable clinical picture and absence of anaemia and macrocytosis. Therefore, a high index of suspicion is needed for the early diagnosis of B12 deficiency in patients with neuropsychiatric disorders to prevent permanent neurological damage, since the response to prompt treatment is satisfactory.

Disclosure Statement

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Competing Interests

Written informed consent obtained from the patient for publication of this case report and any accompanying images.

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