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CASE REPORT

Thalassemia minor presenting with vitamin B_{12} deficiency, paraparesis, and microcytosis

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Arwa Lardhi[1]
Rania Alhaj Ali[1]
Rola Ali[2]
Tarek Mohammed[1]

[1]Internal Medicine Department, Doctor Soliman Fakeeh Hospital, Jeddah, Saudi Arabia; [2]An-Najah National University, Nablus, West Bank, Palestine

Abstract: Vitamin B_{12} is essential for proper neurological functioning, and its deficiency may cause a wide range of neuropsychiatric and hematological manifestations. We report a case of a previously healthy 32-year-old female who was admitted to our hospital with sudden onset of bilateral lower limb paraparesis and loss of sensation. The serum level of vitamin B_{12} was mildly decreased with high methylmalonic acid and homocysteine levels. However, her complete blood count showed no evidence of anemia or macrocytosis; instead, her mean corpuscular volume was low. Hemoglobin electrophoresis showed thalassemia trait, and that probably masked the megaloblastic features of vitamin B_{12} deficiency. She responded fully to vitamin B_{12} replacement therapy.
Keywords: thalassemia trait, microcytosis, pernicious anemia, paraparesis, cobalamin deficiency

Background

Vitamin B_{12} is classified as a water-soluble vitamin that is fundamental for cellular metabolism and appropriate nervous system functioning. Vitamin B_{12} deficiency can lead to inefficient erythropoiesis, megaloblastic anemia, and neuropsychiatric manifestations such as neuropathy, myelopathy, depression, and dementia.[1]

Vitamin B_{12} level is generally evaluated in patients with macrocytic anemia; however, it ought to be remembered that its deficiency in some individuals could be unacknowledged due to other associated conditions as thalassemia minor or iron deficiency that would conceal the macrocytosis.[2]

We present a case of vitamin B_{12} deficiency presenting with sudden onset of paraparesis, normal hemoglobin level, and low mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH).

Case report

A 32-year-old female patient, who was not known to have any medical illness, presented to the emergency with sudden onset of lower limbs paraparesis. She was in her usual state of health until 2 weeks back when she started to complain of recurrent attacks of vertigo, vomiting, and generalized weakness. The patient was not able to move her lower limbs, stand, or walk. It was associated with sensory loss.

There was no history of trauma, visual or speech disorder, or change in her mental status. No suggestive history of autoimmune disease or focus of infection or any source of bleeding was demonstrated. There was no history of change in weight or bowel habits, and she denied any alcohol intake or illicit drug consumption. She was not vegetarian, and there was no drug history.

Correspondence: Rania Alhaj Ali
Internal Medicine Department, Doctor Soliman Fakeeh Hospital, Jeddah, Saudi Arabia
Email dr.rania_2013@hotmail.com

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On physical examination, the patient was pale but not jaundiced. She was conscious, alert, and oriented to place, person, and time. Upon neurological examination, all cranial nerves were intact. The patient was not able to stand or move her lower limbs, with hypotonia, loss of sensation and proprioception, and a power rating of 0/5. On the other hand, her upper limbs had normal tone, intact sensation, and a power rating of 5/5. Reflexes were normal in upper and lower limbs. Babinski sign was negative. Cerebellar examination was normal except for shin-to-heel test and gait, which could not be evaluated. The rest of the examination was unremarkable.

All initial laboratory investigations are shown in Table 1. The patient's hemoglobin electrophoresis was diagnostic for thalassemia trait. Her vitamin B_{12} level was low with high methylmalonic acid and homocysteine.

Lumbar puncture was done, and the analysis was normal. Herpes simplex and oligoclonal antibodies in cerebrospinal fluid (CSF) were negative. MRI of the brain and whole spine was normal. Nerve conduction study was normal.

The patient was initially managed as Guillain Barre syndrome and was prescribed 5 doses of intravenous immunoglobulin. By the end of the investigation, the diagnosis of vitamin B_{12} deficiency was established, and the patient was started on 1 mg of intravenous methylcobalamin (1,000 µg) daily for 10 days, followed by 1 mg intramuscular injection once weekly for another month.

The patient showed immediate response by gradually gaining back her sensation. Therefore, she was discharged with prescription of intramuscular vitamin B_{12} weekly for 2 months and physiotherapy.

One month after commencing treatment, she showed marked improvement in her symptoms and was able to walk with minimal assistance. Neurological examination showed power of 4/5 and mildly decreased sensation in the lower limbs. After 2 months of weekly vitamin B_{12} therapy, she was finally able to walk without assistance.

Eventually, she was diagnosed with pernicious anemia following gastritis on upper endoscopy. A trial of oral vitamin B_{12} was tried, but she failed the treatment because of recurrence of her previous symptoms. Patient resumed her intramuscular injections with complete resolution of symptoms, and she is maintained on a lifelong monthly vitamin B_{12} injection therapy.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consents is available for review by the Editor-in-Chief of this journal.

Discussion

We report a case of cobalamin deficiency in which the diagnosis was delayed because of concomitant thalassemia trait. She was admitted due to sudden-onset lower limb paraparesis and sensory loss. The hemoglobin level was normal with microcytosis and mildly low vitamin B_{12} level. After treatment with B_{12} injections, the patient regained her normal functional status.

Vitamin B_{12} cannot be synthesized in the body; instead it should be ingested from exogenous sources. It is absorbed mainly in the terminal ileum, and its uptake requires an intrinsic factor that is synthesized by gastric parietal cells.[3] Cobalamin is essential for DNA synthesis, erythropoiesis, and the formation and maintenance of myelin sheath. It functions as a cofactor for methionine synthase and L-methylmalonyl-CoA mutase. A deficiency thereby causes elevated homocysteine and methylmalonic acid,[4] as was shown in this patient. Such cases can help in early detection of vitamin B_{12} deficiency as 50% of the patients might have normal B_{12} levels in the blood.[5] Vitamin B_{12} deficiency also has a secondary effect on the enterocytes, leading to more loss of iron storage.[6]

Pernicious anemia is characterized by chronic atrophic gastritis and is the most common cause of vitamin B_{12} deficiency. The gastritis results in the loss of parietal cells in the fundus and body of the stomach due to the presence of specific autoantibodies.[7,8] Two types of antibodies were described, parietal cells and intrinsic factor. The sensitivity of these antibodies in diagnosing pernicious anemia is 90% and 60%, respectively.[9] Upper endoscopy in the case presented showed gastritis with positive antibodies. Therefore, upper endoscopy should be part of the diagnostic workup of vitamin B_{12} deficiency.

Multiple factors can lead to misdiagnosis of vitamin B_{12} deficiency. Many physicians and healthcare providers overlook cobalamin deficiency until the patient develops macrocytic anemia, which is often a late sign of advanced vitamin B_{12} disease.[10] Relying on MCV alone to rule out vitamin B_{12} is not sufficient, as it lacks the sensitivity and specificity for cobalamin deficiency, especially with concurrent conditions such as iron deficiency anemia or thalassemia trait. These conditions lead to absence of macrocytosis; therefore, MCV should not be the only parameter used to diagnose vitamin B_{12} deficiency.[11,12] Another important element that can lead to misdiagnosis of cobalamin deficiency is the absence of anemia despite low levels of vitamin B_{12}, as was shown in a previous study in which only 21.5% of the patients had anemia.[13]

Table 1 Lab investigations at time of presentation

Lab investigation	Result	Normal range
WBC	11.9×10³/μL	4.1–12×10³/μL
Hemoglobin	12.5 g/dL	11.7–15.5 g/dL
MCV	64 fL	80–96 fL
MCH	20 pg	27–33.5 pg
RDW	15.4%	11.7%–14.5%
CRP	0.6 mg/L	0–5 mg/L
Platelets	193×10³/μL	150–400×10³/μL
Creatinine	0.78 mg/dL	0.55–1 mg/dL
Sodium	137 mmol/L	135–145 mmol/L
Potassium	4.7 mmol/L	3.5–5.1 mmol/L
Total creatine kinase	30 U/L	29–168 U/L
Lactate dehydrogenase	154 U/L	125–220 U/L
Ferritin	66.56 ng/mL	4.6–204 ng/mL
Serum iron	50 μmol/L	9–30 μmol/L
Vitamin B_{12}	158 pg/mL	187–883 pg/mL
Homocysteine	14.19 μmol/L	4.4–13.5 μmol/L
Methylmalonic acid	709 nmol/L	87–318 nmol/L
Folic acid	8.9 ng/mL	3.1–20 ng/mL
Hemoglobin electrophoresis		
Hemoglobin A1	94.1%	95%–100%
Hemoglobin A2	5.9%	1%–3.5%
Hemoglobin F	Undetectable	
TSH	1.6 IU/mL	0.33–4.9 IU/mL
CSF cell count		
WBC	1/μL	<5 μ/L
RBC	0/μL	<5 μ/L
CSF chemistry		
Glucose	70 mg/dL	40–70 md/dL
Protein	30 mg/dL	15–45 mg/dL
HSV 1 and 2 in CSF	Not detected	
Oligoclonal band in CSF	Not detected	
CSF cytology	Negative for malignancy	
HIV	Nonreactive	
Antinuclear antibodies	Negative	Negative if <20
Anti-Ds DNA	Negative	
Anti-cardiolipin antibody		
IgG/IgM	2.9/5.3	Negative if <12.5
Lupus anticoagulant	1.19 ratio	0.8–1.2
ANCA	C-ANCA 2.8/P-ANCA 3.8	Negative if <20
β_2 microglobulin	1.7 mg/L	0.97–2.64 mg/L
Parietal cell antibodies	115.2 units	Negative <20 units Equivocal 20.1–24.9 units Positive >25 units
Intrinsic factor antibodies	79/mL	Negative if <20/mL
Gastric biopsy	Negative for malignancy or *Helicobacter pylori*	

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CSF, cerebrospinal fluid; CRP, C-reactive protein; HSV, herpes simplex virus; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; RBC, red blood count; RDW, red blood cell distribution width; TSH, thyroid stimulating hormone; WBC, white blood count.

The patient presented here initially had microcytosis, and thalassemia trait was ultimately diagnosed in this case. Probably this misled the physicians to think of vitamin B_{12} deficiency as a cause of her paraparesis that led to unnecessary invasive procedures and invasive management. Normal vitamin level is one of many conditions that might lead to underdiagnosed B_{12} deficiency, and that is why physicians need to check methylmalonic acid and homocysteine levels before excluding B_{12} deficiency.

Vitamin B_{12} deficiency has been largely ignored in favor of other relevant diagnoses such as diabetic neuropathy, multiple sclerosis, Guillain Barre syndrome, and major depression. Thus,

considering an early diagnosis and promptly initiating treatment is critical to prevent permanent neurologic disability and poor outcomes. Our center reported a similar case of a middle-aged man who was initially diagnosed with organic mood disorder but did not improve on antipsychotics. After further diagnostic workup, severe vitamin B_{12} deficiency was identified and he responded to cobalamin replacement therapy.[14]

As common as vitamin B_{12} deficiency may be, it is possible sometimes for it to be overlooked. The purpose of this case report is to show that vitamin B_{12} deficiency should be considered in the differential diagnosis in patients presenting with paralysis, even in the absence of macrocytosis. It emphasizes the fact that increased MCV is a hallmark in vitamin B_{12} deficiency, but it is not an obligatory sign. Vitamin B_{12} deficiency is a reversible condition; nonetheless, delaying the management can lead to irreversible complications. Consequently, awareness of this fact is vital in early detection, treatment, and prevention.

Disclosure

The authors report no conflicts of interest in this work.

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