

Masked deficit of vitamin B12 in the patient with heterozygous β -thalassemia and spastic paraparesis

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Abstract

The spinal cord, brain, optic nerves and peripheral nerves may be affected by vitamin B12 (cobalamin) deficiency. Deficiency of vitamin B12 also causes megaloblastic anaemia, meaning that the red blood cells are usually larger than normal.

In this paper we report a 16-year old girl who was referred to us for the evaluation of mild paraparesis and paresthesias marked by tingling "pins and needles" feelings and general weakness. The patient, her parents and sisters were on a strict vegan diet, which made us believe that vitamin B12 deficiency may be the possible cause of the neurologic clinical manifestations. The serum level of vitamin B12 was low, but there was no macrocytosis in the routine blood examination.

The electrophoresis of haemoglobin was pathologic, there was 3.7% of HbA2 and 11,6% of HbF (heterozygous form of β -thalassaemia).

When megaloblastic anaemia occurs in combination with a condition that gives rise to microcytic anaemia, many megaloblastic features may be masked. Instead of being macrocytic, the anaemia could be normocytic or even microcytic. Vitamin B12 deficiency is a diagnosis that must not be overlooked. This case report turns the light on the fact that increased MCV is a hallmark in vitamin B12 deficiency, but it is not an obligatory sign.

Key words : β -thalassaemia, vitamin B-12 deficiency.

Introduction

The spinal cord, brain, optic nerves and peripheral nerves may be affected by vitamin B12 (cobalamin) deficiency (Victor M. and Ropper A. H., 2001). Deficiency of vitamin B12 also causes megaloblastic anaemia, meaning that the red blood cells are usually larger than normal, their mean corpuscular volume (MCV) is elevated (norm. values : 83-100 fl) and their maturation is abnormal. The neutrophils are usually large and hypersegmented, and in advanced cases of megaloblastic anaemia caused by vitamin B 12 deficien-

cy neutropenia and thrombocytopenia may also be seen. Macrocytosis, a hallmark of uncomplicated megaloblastic anaemia, may be absent in individuals with either α or β -thalassaemia or iron deficiency anaemia.

Thalassaemias are a heterogenous group of heritable microcytic anaemias of varying degrees of severity which may, also, cause asymptomatic thrombotic events (Engelborghs S. *et al.*, 2003). Underlying genetic defects result in abnormal haemoglobins. Thalassaemia genes are remarkably widespread, and these abnormalities are believed to be among the most prevalent of all human genetic diseases (Nathan D. G. and Orkin S. H., 1998).

Case report

In this paper we report a 16-year old girl who was referred to us for the evaluation of mild paraparesis and paresthesias marked by tingling "pins and needles" feelings and general weakness. The neurologic exam disclosed a disorder of the posterior and lateral columns of the spinal cord, predominantly of the former – loss of vibration sense was by far the most consistent sign. The motor signs were limited to the legs, including a mild symmetrical loss of strength in proximal muscles, loss of ankle jerks, mild spasticity and absent plantar responses.

The patient and her parents were on a strict vegan diet (a diet without animal proteins) which made us believe that vitamin B12 deficiency may be the possible cause of the neurologic clinical manifestations.

The serum level of vitamin B12 was low (30 pmol/L ; norm. 162-694 pmol/L), but there was no macrocytosis in the routine blood examination (MCV was 92 f/l). Other haematologic parameters disclosed mild anaemia : Er $3.81 \times 10^{12}/l$ (n.v. 3.9-5.0), Hb 118 g/l (n.v. 120-157), Hct 0.35 (n.v. 0.36-0.47) MCH 31 pg (n.v. 27-34), thrombocytopenia - Pt $98 \times 10^9/L$ (n.v. 158-424) and mild leucopenia -

WBC $3.3 \times 10^9/L$ (n.v. 3.4-9.3). RDW was increased (23.5%), which reflected erythrocyte populations of different sizes. The reticulocyte count was under normal limits. Homocystein in serum was elevated - 145 $\mu\text{mol/l}$ (n.v. < 16). Excretion of methylmalonic acid in the urine was very high - 0.43 mol/molCr (n.v. < 0.03). In peripheral blood smear anisocytosis and hypersegmented neutrophils were shown. The values of serum ferritin, iron and folic acid were normal, serum lactic dehydrogenase was raised (LDH = 580 U/l, n.v. < 460). The flow cytometer did not show the presence of platelet or neutrophil antibodies, direct and indirect Coombs tests were negative. The bone marrow examination disclosed a hypercellular pattern with megaloblastic erythroblasts, which indicated hyperplastic erythropoiesis. The ratio between myeloid and erythroid precursors was 1:1, metamyelocytes were abnormally shaped and megakaryocytes were hypersegmented.

The electrophoresis of haemoglobin was pathologic, there was 3.7% of HbA2 and 11,6% of HbF. The electrophoresis of the girl's mother's haemoglobin showed very similar results, which is very important for a positive confirmation of β -thalassaemia diagnosis. The neuroradiologic examination (MR of brain and spine) disclosed no changes in the posterior columns of the spinal cord, as was to be expected, probably because it was not an advanced case of myelopathy.

After four weeks of therapy with vitamin B12 a regression of the neurologic and some haematologic symptoms was evident, but the patient had microcytosis (MCV = 69 f/l). RTC, serum ferritin, and iron levels were still normal. After three months of therapy there was no neurologic deficit and the RDW value was normal.

Discussion

We described a 16-year-old girl with heterozygous β -thalassaemia minor and vitamin B12 deficiency who was admitted because of slow progression of mild spastic paraparesis and paresthesias. The level of vitamin B12 in serum was very low, but there was no macrocytosis as one of hallmarks of vitamin B12 deficiency. Electrophoresis of mother's and girl's haemoglobin confirm β -thalassaemia diagnosis.

We found several reports describing masked megaloblastic anaemia in β -thalassaemic patients, but none of them described all three lines of haematopoietic cells below normal values and there were no such neurologic manifestations of vitamin B12 deficiency at the same time (Mazzone A. *et al.*, 2001).

When megaloblastic anaemia occurs in combination with a condition that gives rise to microcytic anaemia, many megaloblastic features may be

masked. Instead of being macrocytic, the anaemia could be normocytic or even microcytic. The most frequent causes of microcytic anaemia are iron deficiency, inflammation and thalassaemias (Bobior B. M., 1990 ; Olivieri N. F., 1999).

The occurrence of anaemia in thalassaemic patients who developed folic acid or vitamin B12 deficiency is usually unrecognised. Women with thalassaemias during pregnancy need more folic acid for normal bone marrow functioning, and folic acid must be supplemented to avoid neural tube defects (Bobior B. M., 1990).

Vitamin B12 deficiency is common, with most patients lacking the classic features of advanced severe deficiency. Early diagnosis and treatment prevent severe anaemia and damage to the nervous system (Pittock S. J. *et al.*, 2002 ; Learner A. J., 2002 ; Teunisse S. *et al.*, 1996).

Vitamin B12 deficiency is a diagnosis that must not be overlooked. This case report turns the light on the fact that increased MCV is a hallmark in vitamin B12 deficiency, but it is not an obligatory sign.

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