CASE REPORT

Severe vitamin B₁₂ deficiency in a 15-year-old boy: presentation with haemolysis and pancytopeniaEbru Yılmaz Keskin,¹ Mahmut Keskin²¹Department of Pediatric Hematology and Oncology, Samsun Education and Research Hospital, Samsun, Turkey²Department of Pediatric Cardiology, Samsun Education and Research Hospital, Samsun, Turkey

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SUMMARY

A 15-year-old boy on a vegetarian diet presented with severe macrocytic anaemia (haemoglobin, 5.1 g/dL; mean corpuscular volume, 116 fL) in addition to leucopenia and thrombocytopenia (pancytopenia), icterus secondary to haemolysis and splenomegaly. Laboratory investigations revealed severe vitamin B₁₂ (cobalamin) deficiency. Following cobalamin replacement therapy, the patient reported increased well-being, including appetite and weight gain, and his icterus resolved. In the follow-up laboratory examinations, leucocyte and platelet counts in addition to serum bilirubin and lactate dehydrogenase levels normalised. At the end of 2 months, laboratory findings, including haemoglobin level, were all within the normal range. We present this case as a reminder that severe vitamin B₁₂ deficiency may present with findings mimicking acute leukaemia (pancytopenia and splenomegaly) and findings suggestive of pseudothrombotic microangiopathy.

BACKGROUND

Inadequate consumption of animal foods and pernicious anaemia (loss of intrinsic factor due to autoimmune atrophic gastritis) are the most common causes of severe vitamin B₁₂ deficiency worldwide in children and adults, respectively.^{1 2}

Vitamin B₁₂ deficiency may cause reversible megaloblastic anaemia and/or demyelinating central nervous system disease. For unclear reasons, the severity of megaloblastic anaemia in vitamin B₁₂-deficient individuals is inversely correlated with the degree of neurological dysfunction.¹

Although most of the vitamin B₁₂-deficient cases have only mild haematological findings, in approximately 10% of patients, life-threatening conditions such as symptomatic pancytopenia, severe anaemia (defined as a haemoglobin level <6 g/dL) and haemolytic anaemia have been reported.³ We report an adolescent boy with severe cobalamin deficiency who consumed inadequate food of animal origin. He presented with severe anaemia, findings of haemolysis and pancytopenia. Haematological findings resolved completely following appropriate replacement therapy.

CASE PRESENTATION

A 15-year-old vegetarian boy born to non-consanguineous parents presented with easy fatigue, breathlessness and pain in the legs on walking, noted during the past few weeks. Paleness and icterus in the sclerae had been noted by the parents for about 2 years, although these findings became more obvious within the last few weeks.

The vegetarian patient had not consumed any food of animal origin for many years. Besides, the family only rarely ate fresh fruits or vegetables.

The patient had a history of an upper respiratory tract infection that began about 15 days earlier and resolved 1 week later. No fever was noted. In the physical examination, the patient looked pale and weak, and his sclerae were icteric. His heart rate was 96 bpm, and a 2/6 mesocardiac systolic murmur was heard.

INVESTIGATIONS

Laboratory investigations revealed severe macrocytic anaemia (haemoglobin 5.1 g/dL; mean corpuscular volume (MCV), 116 fL), leucopenia (white cell count 2540/μL; neutrophil count 1230/μL) and thrombocytopenia (107 000/mm³). Reticulocyte percentage was 0.8%. Serum indirect bilirubin, lactate dehydrogenase (LDH), aspartate and alanine aminotransferases and uric acid levels were 4 mg/dL (0–0.8), 5565 U/L (135–225), 150 U/L (8–40), 51 U/L (8–41) and 8.5 mg/dL (2.4–8), respectively. C reactive protein, direct Coombs and testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency (screening test) were all negative. Serum vitamin B₁₂, folic acid, iron, iron-binding capacity and ferritin levels were 58 pg/mL (211–911), 5.84 ng/mL (3–17), 281 μg/dL (33–193), 6 μg/dL (125–392) and 464 ng/mL (15–200), respectively. Plasma homocysteine level was markedly elevated (>50 μmol/L; normal 5–12 μmol/L). Epstein-Barr virus and cytomegalovirus serologies were both indicative of a past infection (no recent infection). These findings were thought to be consistent with severe vitamin B₁₂ deficiency. Antiendomysial and anti-tissue transglutaminase IgA antibodies for screening celiac sprue, and anti-intrinsic factor (anti-IF) and antiparietal cell antibodies for pernicious anaemia were all negative.

A peripheral blood smear showed anisocytosis and poikilocytosis with macrocytes and small, fragmented red cells (schistocytes) mimicking microangiopathic haemolytic anaemia, in addition to hypersegmented neutrophils. No blastic cells were seen. Abdominal ultrasonography revealed splenomegaly, the vertical margin of the spleen being 130 mm in length (normal <120 mm). ECG and echocardiographic examinations were normal. Bone marrow aspiration study demonstrated macromegalo-erythropoiesis, and ruled out leukaemia.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis, haemolytic anaemia of any cause (ie, G6PD deficiency, autoimmune

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haemolytic anaemia, haemolytic uraemic syndrome, hereditary spherocytosis), haematological malignancy, infectious causes, aplastic anaemia, storage disorders and haemophagocytic lymphohistiocytosis (due to pancytopenia and splenomegaly), vitamin B₁₂ or folic acid deficiency (due to macrocytic anaemia) and autoimmune lymphoproliferative syndrome (due to the combined finding of haemolysis, pancytopenia and splenomegaly) were considered. Bone marrow aspiration study ruled out leukaemia, and the laboratory results consistent with severe vitamin B₁₂ deficiency were thought to explain all the abnormal findings at presentation (severe macrocytic anaemia, pancytopenia, findings of haemolysis and low reticulocyte count).

TREATMENT

As the patient's anaemia was caused by nutritional deficiency, and there was no sign of heart failure, he was not transfused. Intramuscular cyanocobalamin was started (0.5 µg/kg/day for 2 days followed by 100 µg/day for 2 days and 1000 µg/day for 1 week; thereafter, he received 1000 µg cyanocobalamin weekly for 1 month, and would receive it once every month for 6 months). In the second week of therapy, oral iron (ferrous glycine sulfate; 4 mg/kg/day of elemental iron) and folic acid (5 mg/day) were initiated due to the expected increase in iron utilisation and borderline serum folic acid level (tested as 2.8 ng/mL 5 days after treatment initiation), respectively.

OUTCOME AND FOLLOW-UP

The patient reported an increased level of well-being, including a good appetite, only a few days following therapy. Five days after treatment initiation, his haemoglobin, white cell count and neutrophil counts rose to 6.5 g/dL, 5160/µL and 1660/µL, respectively, whereas his platelet count dropped to 91 000/mm³. His serum indirect bilirubin and LDH levels declined to 2.7 mg/dL and 5225 U/L, and plasma homocysteine dropped to 6.3 µmol/L (normal 5.0–12.0 µmol/L). Reticulocytosis was not assessed due to the unavailability of testing at the time. At the end of 2 weeks, thrombocytopenia and indirect hyperbilirubinaemia were found to be resolved. In the follow-up examination at the end of 2 months, the patient was found to have gained weight markedly (due to increased appetite). Laboratory findings performed at that time were all normal (haemoglobin 15.7 g/dL; MCV 86.6 fL; leucocyte count 6710/µL; platelets 255 000/mm³; serum indirect bilirubin 0.3 mg/dL; LDH 179 U/L; aspartate aminotransferase 20 U/L; alanine aminotransferase 11 U/L; uric acid 7.8 mg/dL; iron 69 µg/dL; iron binding capacity 230 µg/dL; ferritin 168 ng/mL; vitamin B₁₂ 318 ng/mL; folic acid 10.1 ng/mL and plasma homocysteine 7.8 µmol/L).

DISCUSSION

In humans, vitamin B₁₂ is needed as a cofactor for two reactions: methylcobalamin is the cofactor for the cytoplasmic enzyme, methionine synthase, while adenosylcobalamin is the cofactor for the mitochondrial enzyme, methylmalonyl coenzyme A mutase. Hence, vitamin B₁₂ deficiency results in the accumulation of homocysteine and methylmalonic acid. Cobalamin is essential for DNA synthesis, haematopoiesis and myelination.^{1 2 4}

Since humans cannot synthesise vitamin B₁₂, it needs to be ingested in the diet from foods of animal origin. The most common cause of cobalamin deficiency in infants and children is inadequate consumption due to dietary restriction or lack of access to animal-sourced food.² Cobalamin stores last for several years after restriction of intake or malabsorption.¹ Our 15-year-old boy had consumed no meat, poultry, fish, eggs, milk

or other dairy products for years, which well explains his severe vitamin B₁₂ deficiency status.

In a study including 201 adults with well-documented cobalamin deficiency, approximately 10% of the patients were found to have life-threatening haematological manifestations.³ Among these were pancytopenia (5%), severe anaemia (defined as a haemoglobin level <6.0 g/dL; 2.5%) and haemolytic anaemia (1.5%). Our patient had severe macrocytic anaemia, pancytopenia and findings of haemolysis (fragmented, misshapen cells in the peripheral smear mimicking microangiopathic haemolytic anaemia, indirect hyperbilirubinaemia and marked increase in LDH). Notably, reticulocyte count at admission was low. Concurrent haemolysis in patients with vitamin B₁₂ deficiency is a well-recognised phenomenon and has been attributed mainly to intramedullary destruction of erythrocytes (ineffective erythropoiesis).⁵ In their study comparing patients with pseudo-thrombotic microangiopathy (pseudo-TMA) due to vitamin B₁₂ deprivation patients with thrombotic thrombocytopenic purpura (TTP), Noël *et al* always found the reticulocyte count to be low in pseudo-TMA cases in contrast to patients with TTP, and concluded that in a patient with mechanical haemolysis accompanied by thrombocytopenia, very high LDH levels and a low reticulocyte count, strongly suggest pseudo-TMA and cobalamin deficiency as possible underlying cause. The combination of a low reticulocyte count and markedly elevated LDH levels is suggestive of intramedullary haemolysis.

The parents of our patient had noted overall paleness and icterus in their son's sclerae for about 2 years, which became more obvious during the last few weeks. A viral infection may have aggravated the haemolytic process. However, the low reticulocyte count at admission points to intramedullary haemolysis (due to cobalamin deficiency) rather than haemolysis due to an infection.

In addition to intramedullary haemolysis due to ineffective erythropoiesis, homocysteine accumulation due to vitamin B₁₂ or folate deficiency was found to increase haemolysis *in vitro*.^{6 7} Plasma homocysteine concentration was found markedly elevated (>50 µmol/L) in our patient, and declined to normal within 1 week of cobalamin replacement.

Cobalamin is essential for DNA synthesis and haematopoiesis, and its severe deficiency not only causes megaloblastic anaemia, but may also result in thrombocytopenia and leucopenia (neutropenia), as in our patient.^{8–10} Splenomegaly and/or hepatomegaly have also been reported in cases with severe cobalamin deficiency.⁸ Hepatosplenomegaly in these patients may be attributed to increased extramedullary haematopoiesis compensatory to haemolytic anaemia complicating nutritional cobalamin deficiency.

Owing to the remarkable dietary history of our patient, we thought inadequate dietary intake to be the cause of cobalamin deficiency. However, the patient is 15 years of age, and pernicious anaemia has been reported as the most common cause of severe cobalamin deficiency in adults.^{1 3 5} Additionally, pseudo-TMA associated with cobalamin deficiency has been reported most frequently in adults with pernicious anaemia rather than in those with malabsorption or dietary insufficiency.^{3 5} In cobalamin-deficient individuals, the identification of the underlying cause is important, as the management is distinct in different conditions (in dietary deficiency, a change in diet habits can improve serum vitamin B₁₂ levels and eliminate the need for intramuscular cobalamin injections, whereas in pernicious anaemia, lifelong treatment is indicated). Testing for anti-IF and antiparietal cell antibodies were negative in our case, the sensitivities of which are 50% and 80% for pernicious

anaemia, respectively.¹ Chronic atrophic gastritis may also cause cobalamin deficiency, and it can be diagnosed on the basis of an elevated fasting serum gastrin level and a low level of serum pepsinogen I.¹ Some authors recommend endoscopic examination to confirm gastritis and rule out gastric tumours, since patients with pernicious anaemia are at increased risk for such cancers. As our patient had been on a vegetarian diet for years, and anti-IF and antiparietal cell antibodies were found negative, no endoscopic examination was performed.

We have described a patient with nutritional cobalamin deficiency who presented with severe anaemia, haemolysis and

findings mimicking acute leukaemia (pancytopenia and splenomegaly). Care givers should be aware of these possible presentations secondary to vitamin B₁₂ deficiency, particularly in high-risk populations. Besides, appropriate treatment provides rapid resolution of the associated signs and symptoms.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ Inadequate intake of vitamin B₁₂ is the most common cause of vitamin B₁₂ deficiency in children.
- ▶ Vitamin B₁₂ deficiency may present with findings mimicking acute leukaemia (ie, pancytopenia and organomegaly).
- ▶ Severe vitamin B₁₂ deficiency may cause haemolytic anaemia, which may be mainly explained by ineffective erythropoiesis and elevated homocysteine levels.
- ▶ In the presence of mechanical haemolysis and thrombocytopaenia, the combination of markedly elevated lactate dehydrogenase levels and a low reticulocyte count, are strongly suggestive of pseudothrombotic microangiopathy and cobalamin deficiency as the possible underlying cause.
- ▶ Appropriate treatment results in rapid resolution of associated symptoms and of abnormal laboratory findings.

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