CASE REPORT

Copper deficiency as a cause of neutropenia in a case of coeliac disease

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SUMMARY

We report a 17 year-old male patient, who presented with chronic diarrhoea, progressive pallor, short stature, anaemia (haemoglobin of 4.9 g/dL) and neutropenia and was diagnosed as coeliac disease. His neutropenia did not respond to 8 months of gluten-free diet, iron, folic acid and vitamin B₁₂ therapy. So we suspected copper deficiency and his serum copper levels were tested, which was low. His neutrophil counts normalised after 2 months of copper supplementation. Hence we concluded that the cause of neutropenia in our case was copper deficiency.

BACKGROUND

Haematological abnormalities in coeliac disease (CD) are well known. Neutropenia in CD in children due to copper deficiency has rarely been reported.

CASE PRESENTATION

CD has a wide variety of clinical presentations. Along with the 'classical CD', in which malabsorption is prevalent, there are 'non-classical CD' without symptoms of malabsorption suggesting multisystemic involvement in CD.¹ Severe iron, folic acid, vitamin B₁₂ and/or copper deficiency can result in anaemia, decrease in leucocytes and platelets and even manifest as severe pancytopenia.²

A 17 year-old male patient presented with history of recurrent episodes of loose stools and inadequate weight gain since the age of 1 year. Loose stools were bulky and foul smelling, occurring 5–6 times per day. He also had history of progressive pallor and anorexia since 6 years. He was a non-vegetarian in dietary habits. He did not have history of excessive zinc intake. On examination, his weight was 26.6 kg (<3rd centile as per Centre for Disease Control and Prevention (CDC) standards for growth) and height was 145.5 cm (<3rd centile as per CDC standards for growth). He had severe pallor, enlarged spleen (palpable until 2 cm below left costal margin) and normal liver span. There were no symptoms and signs of neuropathy, myelopathy, vision loss or any neurological disorder and his intellectual abilities were also normal. He had age-appropriate pubertal development. Rest of the systemic examination was unremarkable. The review of his investigations carried out over the past 9 years revealed severe iron deficiency anaemia (refractory to oral iron supplements 6 mg/kg/day), no blood loss or worms in stools. Haemoglobin (Hb) electrophoresis was normal. His Hb value

ranged between 4.5 and 6.1 g/dL, total leucocyte count (TLC) varied between 2600/mm³ and 3000/mm³ with absolute neutrophil count (ANC) varying from 1100/mm³ to 1200/mm³ and serum tissue transglutaminase (tTG) IgA was normal (8.63 U/mL). The investigations performed at our institute are shown in table 1.

Peripheral blood smear revealed a dimorphic picture. His serum ferritin was 39 ng/mL (normal range 28–397 ng/mL), ultrasonography of the abdomen revealed normal liver and enlarged spleen with 13 cm length. Serum calcium, renal and liver function tests were within normal limits. Our provisional diagnosis was malabsorption with short stature with dimorphic anaemia and neutropenia. His serum folic acid level was 10 ng/mL (normal range 2–20 ng/mL) and vitamin B₁₂ levels was 90 pg/mL (normal range 150–750 pg/mL).

TREATMENT

The patient received oral iron (6 mg/kg), folic acid (2.5 mg daily) and vitamin B₁₂ therapy. He was administered vitamin B₁₂ injection 1000 µg intramuscular daily for 2 weeks and then weekly for 2 months.

OUTCOME AND FOLLOW-UP

Following 2 months of treatment, anaemia and neutropenia were persisting (Hb 4.9 g/dL, TLC 2600/mm³ and ANC 1136/mm³). In view of non-response to haematinics, the diagnosis was reviewed. The repeat IgA tTG was 257 U/mL (normal <10 U/mL). Duodenal biopsy revealed subtotal villous atrophy with crypt hyperplasia, increased intraepithelial lymphocytes with increased inflammation of lamina propria (Marsh III).³ Based on the clinical profile and laboratory findings, diagnosis of CD was made. Along with strict gluten-free diet (GFD), iron, folic acid, multi-vitamins supplements and parenteral vitamin B₁₂ were continued. After 5 months of good compliance of GFD, his Hb improved to 9.3 g/dL but neutropenia persisted (TLC=3400/mm³ and ANC=1300/mm³). Bone marrow aspiration revealed normoblastic erythropoiesis with mild megaloblastoid change. After 8 months of GFD, iron, folate and parenteral vitamin B₁₂ therapy his weight increased by 11 kg and his height increased by 6 cm, but his neutropenia persisted. So we advised testing of vitamin B₁₂ levels, which were reported to be normal (250 pg/mL). The tTG tests were repeated which were normal thus showing good compliance to GFD. We then advised to test serum copper level. It was low at 4 µmol/L (normal

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Table 1 Haematological parameters of the patient on gluten-free diet and supplements

Haematological parameters	Before treatment	Duration of follow-up on gluten-free diet and supplements		
		5 months	8 months	10 months
Hb* (12–16.1 g/dL)	4.9	9.3	10.2	12.6
TLC† (4000–10 500/mm ³)	2600	3400	3450	5800
ANC‡ (3000–5800/mm ³)	1136	1300	1330	2400
Platelets (1.5–4.0×10 ³ /μL)	2.16	2.15	2	1.98
Reticulocyte count (0.5–1% of RBCs)	1%	–	–	–
ESR§ (0–10 mm/hour)	25	–	–	–
MCV¶ (78–95 fl)	55.2	59	64	67.2
MCH** (26–32 pg)	14.6	16.6	19.4	21.5
MCHC†† (32–36 g/dL)	26.4	28.2	29.6	30.4
RDW‡‡ (11.5–14.5%)	24.5	21.9	20.5	18.2

*Hb is the haemoglobin.

†TLC is the total leucocyte count.

‡ANC is the absolute neutrophil count.

§ESR is the erythrocyte sedimentation rate.

¶MCV is the mean corpuscular volume.

**MCH is the mean corpuscular haemoglobin.

††MCHC is the mean corpuscular haemoglobin concentration.

‡‡RDW is the red cell distribution width.

RBC, red blood cells.

range 11–24 μmol/L). Serum ceruloplasmin test was, however, not performed due to financial constraints. Hence the child was started on multivitamins containing copper (copper sulfate=3.34 mg each tablet) 1 tablet two times a day and was advised diet rich in copper. After 2 months of copper supplementation his Hb rose to 12.6 g/dL and neutropenia improved (TLC=5800/mm³ and ANC=2400/mm³). So we concluded that neutropenia in our patient was due to copper deficiency, which initially did not respond to GFD, iron, folate and vitamin B₁₂ therapy.

DISCUSSION

CD is known to have multiple haematological manifestations such as anaemia, thrombocytosis, thrombocytopenia, leucopenia/neutropenia, venous thromboembolism, coagulopathy, hyposplenism, IgA deficiency and lymphoma.² The prevalence of anaemia in CD varies greatly and has been found in 12–69% of newly diagnosed patients with CD.^{4–5} Anaemia is the most frequent extraintestinal manifestation in CD.⁶ Clinical features, anaemia, thrombocytopenia and leucopenia reverse after strict GFD in 3 weeks to 8 months duration.^{7–9} In our case anaemia and leucopenia persisted for a long duration despite strict GFD and reversal of other clinical features. In authors' knowledge, there are very few articles which have reported anaemia and neutropenia/leucopenia^{10–11} and some case reports which have reported pancytopenia in CD in children.^{7–9} There are very few case reports on copper deficiency in CD leading to neutropenia.¹¹ Bansal *et al*¹⁰ studied 83 patients with CD and found that 81 (98%) children had anaemia (Hb <11 g/dL) and 6 (8%) patients had leucopenia, out of which 2 had neutropenia. Of the 22 children with CD studied by Fisgin *et al*¹¹ anaemia alone was present in 86.3%, leucopenia coexisted with anaemia in 9%, thrombocytopenia in 4.5%. According to Çatal *et al*¹² of 91 children included in the study, 32 patients (35.2%) had haematological signs at the time of diagnosis. Anaemia (24.2%) was the most common haematological sign, followed by thrombocytosis (16.5%) and leucopenia (4.4%).

Goyens *et al*¹³ diagnosed CD in two unrelated infants aged 7 and 7.5 months with severe malnutrition. Both infants showed

typical clinical and histological signs of CD. Moreover, accompanying copper deficiency was suggested by severe hypocupremia and persistent neutropenia. Rapid and complete correction of these anomalies occurred after the addition of oral copper sulfate to the GFD.

The cause of pancytopenia in CD is multifactorial such as deficiency of one or more nutrients, immunological dysfunction or both. Severe deficiency of iron, folic acid, vitamin B₁₂ and other nutrients can lead to pancytopenia.² In CD, folate deficiency occurs in around 31% of cases and vitamin B₁₂ deficiency occurs in 8–41% of patients.² Copper deficiency has been described in adults and children with CD and may result in anaemia, leucopenia and thrombocytopenia.⁸

Inadequate dietary copper intake infrequently leads to copper deficiency; however, numerous risk factors can impede adequate copper uptake. These include gastrointestinal tract surgery, zinc excess, prolonged total parenteral nutrition and malabsorption enteropathies.¹⁴ Patients with microcytic hypochromic anaemia refractory to iron replacement therapy may actually have hypocupremia. Deficiency of this trace element can also cause myelopathy that presents as subacute combined degeneration of the spinal cord, which is usually attributed to inadequate vitamin B₁₂.¹⁵

The normal range of serum copper level is 11–24 μmol/L. A single subnormal result of serum copper alone is generally sufficient to make a diagnosis of hypocupremia, but marginal copper deficiency may go undetected. If serum copper levels remain normal despite symptoms that suggest copper deficiency, measurement of ceruloplasmin levels can prove useful.¹⁶ After copper replacement therapy, haematological derangements promptly normalise within 1–3 months.¹⁷ Dietary copper can be found in whole grain cereals, legumes, oysters, organ meats (particularly liver), cherries, dark chocolate, fruits, leafy green vegetables, nuts, poultry, prunes and soybean products such as tofu.

In conclusion, neutropenia can be a feature of CD. Strict GFD is the main stay of the treatment. Some patients need prolonged supplementation of specific nutrients such as copper to correct the haematological abnormalities.

Learning points

- ▶ The cause of pancytopenia in coeliac disease is multifactorial such as deficiency of one or more nutrients, immunological dysfunction or both.
- ▶ Strict gluten-free diet is the main stay of treatment.
- ▶ Copper deficiency should be considered in neutropenia in a case of coeliac disease.
- ▶ Some patients need prolonged supplementation of specific nutrients such as copper to correct the haematological abnormalities.

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