CASE REPORT

Vitamin B₁₂ deficiency: unusual cause of jaundice in an adolescent

Phalguna Kousika Katakam,¹ Asha P Hegde,² Manju Venkataramaiahya²

¹Department of Paediatrics, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

²Department of Paediatrics, Melaka-Manipal Medical College, Manipal Academy of Higher Education, Manipal, Udupi, Karnataka, India

Correspondence to

Dr Phalguna Kousika Katakam, phalguna.kousika@manipal.edu

Accepted 14 December 2017

SUMMARY

Vitamin B₁₂ deficiency in vegans is a known cause of megaloblastic anaemia. We report an adolescent girl who presented with jaundice and weight loss for 6 months secondary to vitamin B₁₂ deficiency, leading to megaloblastic anaemia. Replacement with vitamin B₁₂ reversed her symptoms, resulting in weight gain, and normalised her haemoglobin, red blood cell morphology, bilirubin levels and serum vitamin B₁₂ levels.

BACKGROUND

Vitamin B₁₂ deficiency is known to cause haematological and neurological disease. The risk of deficiency is more in vegans when compared with non-vegetarians.¹ Anaemia usually presents as easy fatigability and pallor with investigations showing moderate to severe anaemia or pancytopenia, macrocytic red blood cells and hypersegmented neutrophils on peripheral smear. The neurological disease presents commonly with complaints of tingling sensation of extremities, weakness of lower limbs and features of subacute combined degeneration of cord. Atypical presentation in infants and children includes incidentally detected megaloblastic anaemia, ataxia, failure to thrive, neuroregression, psychiatric manifestations and developmental delay.

There is a lack of consensus on the management of vitamin B₁₂ deficiency in children. Oral administration of cobalamin in large doses is preferred, even in the presence of defective intestinal absorption. Monthly intramuscular injection of cobalamin in adults has shown good disease control results. However, lack of compliance to treatment, either by oral or injectable, is a hindrance to efficient management.

We report this case to emphasise the atypical presentation of vitamin B₁₂ deficiency as chronic jaundice associated with loss of weight, which mimicked chronic liver disease and also to highlight the importance of counselling to ensure drug compliance.

CASE PRESENTATION

A 12-year-old girl presented with complaints of yellowish discolouration of eyes and palms and loss of appetite associated with weight loss for the past 6 months. She also reported easy fatigability for the past 2 weeks. She had no history of abdominal pain, pale stools or bone pain. She had no history of substance abuse, blood transfusions or drug intake.

She attained menarche a year back and has had no menstrual complaints. Parents reported that she has been on a vegetarian diet for the past 2 years due to food faddism. Her birth history, developmental history and family history were unremarkable. She was moderately built, with a body mass index (BMI) of 14.6 kg/m², and physical examination showed icterus, mild pallor, normal liver span and no splenomegaly. Respiratory, cardiovascular and central nervous system examination was essentially normal. The ophthalmic evaluation did not reveal Kayser-Fleischer rings.

INVESTIGATIONS

She was initially evaluated for jaundice. She had anaemia (haemoglobin: 9.4 g/dL; haematocrit: 28.3%), decreased red blood cell (RBC) count ($2.37 \times 10^{12}/L$), increased red cell volume (mean corpuscular volume 119.8 fL), elevated red cell distribution width (16.7%), reticulocytosis (2.25%), elevated lactate dehydrogenase (LDH; 729 IU/L), elevated unconjugated bilirubin (total bilirubin: 7.5 mg/dL, direct bilirubin: 0.6 mg/dL), normal liver enzymes and normal random blood sugar. Peripheral smear showed macrocytosis, occasional spherocytes, predominant neutrophil count (80%) with hypersegmented forms (figure 1) and other cell lines in normal limits. Folate levels and iron studies were normal. Serum vitamin B₁₂ assay showed very low levels (<30 pg/mL), confirming the diagnosis. She also had urine albuminuria, which, in repeat samples, was negative. Other common causes of prolonged jaundice in this age group, like hepatitis A, hepatitis B and Wilson disease, were ruled out by investigations. Repeat investigations, after 6 months of oral therapy with vitamin B₁₂ (1500 µg/day) persisted to show macrocytosis, hypersegmented neutrophils borderline unconjugated bilirubinaemia, normal haemoglobin and improving vitamin B₁₂ levels (82.3 pg/mL). Investigations done 10 months after initial presentation showed haemoglobin, reticulocyte count, bilirubin, LDH and serum vitamin B₁₂ within normal limits. Peripheral smear showed a normal morphology of neutrophils and RBCs.

DIFFERENTIAL DIAGNOSIS

Viral hepatitis followed by chronic liver disease presents with a prolonged history of jaundice and weight loss. Hepatolenticular disease (Wilson disease) can also present as a chronic jaundice. Imerslund-Gräsbeck syndrome is a rare autosomal

CrossMark

To cite: Katakam PK, Hegde AP, Venkataramaiahya M. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222302

Figure 1 Peripheral smear showing hypersegmented neutrophils in an adolescent with vitamin B₁₂ deficiency.

recessive disease that presents with vitamin B₁₂ deficiency and proteinuria. It usually affects children due to a defect in receptor vitamin B₁₂ intrinsic factor complex of the ileal enterocyte.²

TREATMENT

She was started on oral cobalamin at a dosage of 1500 µg/day, folate at 5 mg/day and iron sulfate at 200 mg/day, given as a combination medication. Her compliance was poor, and she was lost for follow-up for 6 months. During this period, she resumed her non-vegetarian diet. Monthly injectable vitamin B₁₂ was offered to the patient; however, family denied the same. Oral drug compliance was ensured by counselling the patient and family. Ten months after the first presentation, she reported significant improvement in well-being, and repeat investigations showed normal serum vitamin B₁₂ levels. However, as compliance to daily oral vitamin B₁₂ treatment was poor, they were counselled for an intramuscular monthly dose of vitamin B₁₂.

OUTCOME AND FOLLOW-UP

Treatment with methylcobalamin reversed the child's symptoms. With cobalamin therapy and dietary changes, she reported improvement in activity and appetite and a weight gain of 10 kg. Her BMI increased from 14 to 18.3 kg/m². Her jaundice resolved and she is under regular follow-up.

DISCUSSION

Vitamin B₁₂, a water-soluble vitamin, has a crucial role in DNA synthesis and erythropoiesis. Deficiency of vitamin B₁₂ causes impaired DNA synthesis due to inhibition of purine and thymidylate syntheses. Vitamin B₁₂ deficiency leads to a state of ineffective erythropoiesis, and its sequelae lead to premature death of erythroblasts in marrow and macrocytes in the peripheral circulation, leading to anaemia.^{3,4} Due to haemolysis, mildly elevated levels of indirect bilirubin are commonly found; however, high bilirubin levels are rarely reported. In our case, high levels of indirect bilirubin were observed at presentation.

High suspicion is required for early diagnosis, detection and management. Deficiency state is common in strict vegetarians, as the major source of dietary vitamin B₁₂ is from animal sources. Peripheral smear, a simple investigation, shows altered RBC morphology and hypersegmented neutrophils in a majority of cases. Serum vitamin B₁₂ assays show low levels even in

asymptomatic children, suggesting false positive low levels.⁵ However, in patients with subtle symptoms and suboptimal levels of vitamin B₁₂, elevated levels of methylmalonic acid assay is found to be useful in establishing disease.⁶

There is no consensus on dosage and mode of administration of cobalamin in children with vitamin B₁₂ deficiency. A recommended dietary allowance (RDA) for children less than 14 years of age is lacking. An RDA of 2.4 µg/day is recommended for children more than 14 years old and adults.⁷ High oral doses up to 1000 times the daily requirement are required in the treatment of deficiency state. However, studies specific to adolescent population are lacking. A few studies suggest oral route of administration as effective as parenteral administration, even in the presence of malabsorption.^{8–10}

Symptoms of the disease are reversible in a majority of patients with haematological disease. The duration taken to reverse symptoms is variable and was 3–4 weeks in our case. Response to therapy is immediately evident by increasing reticulocytes and normalising RBC indices. The neurological disease often is irreversible; however, improvement depends on the severity of symptoms at presentation.⁵

Poor compliance to drug regimens in adolescents is common and is secondary to multiple factors. Effective management of the condition is possible only with good drug compliance.¹¹ Compliance is achieved by motivation, explaining the disease severity and probability of recurrence of symptoms due to poor adherence to medication to the individual and also the family.¹²

Patient's perspective

It was a painful period for me when I had yellowish discolouration of eyes, skin and urine. I was not able to perform any activity I could otherwise do. My school grades came down and my parents were anxious too. Until I was evaluated and they found out that low vitamin B₁₂ could be the cause of my illness, I did not realise my food habits had such a bad effect. I used to avoid non-vegetarian food, milk and vegetables in my diet. Once my treatment was started I readily felt relieved and started gaining confidence at my school. However, it was difficult for me to take a tablet every day and at times I was not willing to take any more medication. My physicians repeated blood tests and explained why it is important to be on medications and they offered me monthly injections. Now I am doing well at school and score the top mark in my class.

Learning points

- ▶ Long-standing jaundice can be a manifestation of vitamin B₁₂ deficiency secondary to ineffective erythropoiesis.
- ▶ There is a need for establishment of treatment guidelines for vitamin B₁₂ deficiency in children.
- ▶ Treatment with high doses of vitamin B₁₂ (either oral or parenteral or both in combination) reverses the symptoms and indices of haematological disease.
- ▶ Ensuring compliance to treatment plays a major role in the management of vitamin B₁₂ deficiency, especially in adolescents.

Contributors PKK, APH and MV identified and came to the diagnosis and initiated the management. PKK initiated the idea of reporting such a rare presentation and was involved in the preparation of manuscript. APH has given her valuable inputs in preparation of the manuscript and had reviewed the same before submission.

Competing interests None declared.

Patient consent Guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Pawlak R, Lester SE, Babatunde T. The prevalence of cobalamin deficiency among vegetarians assessed by serum vitamin B12: a review of literature. *Eur J Clin Nutr* 2014;68:541–8.
- 2 Gräsbeck R. Imerslund-Gräsbeck syndrome (selective vitamin B(12) malabsorption with proteinuria). *Orphanet J Rare Dis* 2006;1:17.
- 3 Koury MJ, Ponka P. New insights into erythropoiesis: the roles of folate, vitamin B12, and iron. *Annu Rev Nutr* 2004;24:105–31.
- 4 Oh R, Brown DL. Vitamin B12 deficiency. *Am Fam Physician* 2003;67:979–86.
- 5 Green R, Datta Mitra A. Megaloblastic anemias: nutritional and other causes. *Med Clin North Am* 2017;101:297–317.
- 6 Harrington DJ. Laboratory assessment of vitamin B12 status. *J Clin Pathol* 2017;70:168–73.
- 7 Eldridge AL. Comparison of 1989 RDAs and DRIs for water-soluble vitamins. *Nutr Today* 2004;39:88–93.
- 8 Altay C, Cetin M. Oral treatment in selective vitamin B12 malabsorption. *J Pediatr Hematol Oncol* 1997;19:245–6.
- 9 Gomollón F, Gargallo CJ, Muñoz JF, et al. Oral cyanocobalamin is effective in the treatment of vitamin B12 deficiency in Crohn's disease. *Nutrients* 2017;9:308.
- 10 Butler CC, Vidal-Alaball J, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. *Fam Pract* 2006;23:279–85.
- 11 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487–97.
- 12 Staples B, Bravender T. Drug compliance in adolescents. *Pediatric Drugs* 2002;4:503–13.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow