



An unusual cause for recurrent jaundice in an otherwise healthy male

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CASE REPORT

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Abstract

A 41-year-old Asian-Indian male presented with recurrent episodes of jaundice over the past six months. Physical examination was normal, barring mild icterus. Laboratory parameters revealed indirect hyperbilirubinemia. Further evaluation yielded a diagnosis of severe nutritional vitamin B12 deficiency. Indirect hyperbilirubinemia was ascribed to ineffective erythropoiesis. Underlying Gilbert's syndrome was ruled out by provocative testing with lipid-restricted diet. Presentation of severe vitamin B12 deficiency with isolated hyperbilirubinemia without concomitant major haematologic or neurologic dysfunction is unusual and potentially underdiagnosed. Awareness of this possibility can permit early diagnosis of vitamin B12 deficiency and forestall development of severe haematologic and neurologic sequelae.

Key Words

Recurrent jaundice; indirect hyperbilirubinemia; vitamin B12 deficiency; ineffective erythropoiesis

Implications for Practice

1. Nutritional vitamin B12 deficiency is seen almost exclusively in vegans, and can manifest with a wide range of haematologic and neurologic symptoms and signs.
2. Vitamin B12 deficiency can also present with isolated recurrent episodes of jaundice.
3. All patients presenting with unexplained indirect hyperbilirubinemia should be screened for vitamin B12

deficiency, especially when associated with other risk factors for the same.

Background

Asymptomatic or minimally symptomatic indirect hyperbilirubinemia can occur in a variety of disorders including haemolytic anaemias such as hereditary spherocytosis and elliptocytosis, and Gilbert's syndrome. Therefore, evaluation of patients with indirect hyperbilirubinemia must include a careful search for evidence of haemolysis, such as elevated serum lactate dehydrogenase (LDH), reticulocytosis and undetectable serum haptoglobin levels. In addition, such patients often exhibit clinical findings of pallor and splenomegaly, although these signs may be subtle or altogether absent in cases of mild haemolysis with brisk compensatory reticulocytosis.

Vitamin B12 deficiency is unique in that it represents an acquired and readily correctable cause for haemolysis. The mechanism of haemolysis in this condition is the phenomenon of ineffective erythropoiesis,¹ wherein immature erythrocytes are lysed within the bone marrow itself, resulting in the release of excess quantities of biliverdin, which is ultimately converted to indirect bilirubin. The resulting clinical picture may be indistinguishable from other forms of haemolytic anaemia, unless accompanied by neurological manifestations of vitamin B12 deficiency. Haematological parameters including a high mean corpuscular volume (MCV) and a macrocytic peripheral blood picture are useful red flags suggesting underlying B12 deficiency in such cases. The absence of reticulocytosis is also a useful marker to distinguish vitamin B12 deficiency – a hypoproliferative state, from true haemolytic anaemias. Low serum B12 in association with these features confirms a diagnosis of vitamin B12 deficiency.

Gilbert's syndrome is another differential diagnosis of isolated asymptomatic hyperbilirubinemia, and is diagnosed by estimation of hyperbilirubinemia after suppression with phenobarbitone and after caloric restriction,² and lipid restriction,⁴ as was performed for our patient. Genetic testing for Gilbert's syndrome is also available.⁴



Case details

A 41-year-old previously healthy Asian-Indian male presented with complaints of recurrent episodes of yellowish discolouration of the eyes over the past six months. He denied any associated symptoms of hepatitis such as anorexia, abdominal discomfort, passage of pale stools or pruritis. There was no history of fever prior to onset of jaundice. The patient also denied any history of substance abuse. At presentation the patient appeared well nourished with no obvious signs of malnutrition including glossitis, stomatitis and angular cheilitis. General physical examination revealed mild icterus and no pallor. Abdominal examination did not show any organomegaly. Neurological examination was normal with no signs of peripheral neuropathy. Routine laboratory work-up showed mild indirect hyperbilirubinemia (Total bilirubin 1.8 mg/dL (normal range 0.3-1.2 mg/dL), direct bilirubin 0.5 mg/dL (normal range 0.1-0.5 mg/dL)). Liver enzymes, serum albumin and prothrombin time were within normal limits. Complete blood counts and ESR were also normal (Haemoglobin: 13.3 g/dL). Serum LDH was slightly elevated (289 IU/L). RBC indices revealed increased mean corpuscular volume (MCV) (119.4 fL), peripheral smear showed predominantly normochromic normocytic erythrocytes with occasional macrocytes. On further work-up serum vitamin B12 levels were found to be low (40.9 pg/mL; normal range 220-800 pg/mL) by chemiluminescence method.⁵ Serum folate levels were normal (8.6 ng/mL). Nerve conduction studies performed were normal, ruling out subclinical peripheral neuropathy.

Retrospective questioning revealed that the patient was a vegan. A diagnosis of indirect hyperbilirubinemia secondary to vitamin B12 deficiency induced ineffective erythropoiesis was made. He was subsequently initiated on parenteral vitamin B12 supplementation. Laboratory parameters repeated after one month showed complete resolution of hyperbilirubinemia and normalisation of MCV. Indirect bilirubin repeated after 48 hours of lipid free diet showed no increase, rendering underlying Gilbert's syndrome unlikely.

Discussion

Nutritional vitamin B12 deficiency is seen almost exclusively in strict vegetarians or vegans.⁶ It is particularly common in India,⁷ where a large proportion of the population adhere to a strictly vegetarian diet on religious or financial grounds. Other important causes of vitamin B12 deficiency include pernicious anaemia due to intrinsic factor deficiency, post-gastrectomy status, bacterial overgrowth and blind-loop syndrome, ileal resection, Crohn's disease, fish tapeworm infestation, and prolonged therapy with proton-pump

inhibitors, anti-epileptics and metformin.⁸

Vitamin B12 deficiency can manifest with a wide span of signs and symptoms.⁶ Broadly, these clinical presentations can be classified into haematologic and neurologic disease.

The principal hematologic complication of vitamin B12 deficiency is megaloblastic anaemia, characterised macrocytes in the peripheral blood smear, and megaloblasts in the bone marrow.⁹ Other blood cell lines may also be involved, producing pancytopenia in the peripheral blood and trilineage dysplasia in the bone marrow.¹⁰ While features of haemolysis can occur due to ineffective erythropoiesis, these are usually seen in association with overt anaemia. Our patient however did not have anaemia at all, suggesting that haemolysis in vitamin B12 deficiency can antedate development of anaemia.

Neurologic disease in vitamin B12 deficiency can range from subtle personality disorders to reversible dementia, and non-compressive myelopathy to peripheral neuropathy.¹¹

Interestingly, some individuals with neurologic disease display only minor hematologic involvement,¹² while patients with severe haematologic disease may have no neurologic disease.¹³ The reasons for such dichotomy remain unclear.

Once deficiency has been diagnosed, vitamin B12 replacement can be attempted through either oral or parenteral routes. While the parenteral route has been standard practice for decades,¹⁴ there is gathering evidence that the oral route of administration might be adequate with larger doses of B12. A recent systematic review by Butler et al,¹⁵ found the two routes to be equally efficacious. The only drawback of this observation was the limited number of individuals enrolled in the randomised controlled trials included in the systematic review, as noted by Butler et al. In our case, we preferred to employ the parenteral route in order to avoid problems with inconsistent absorption.

The variable clinical features of B12 deficiency necessitate a high index of suspicion in populations at increased risk of deficiency. A careful review of available medical literature did not yield any previous reports of severe B12 deficiency presenting with isolated indirect hyperbilirubinemia without concomitant significant hematologic or neurologic involvement. This finding in itself emphasises the need to raise awareness of this presentation among physicians.

In conclusion, screening of vulnerable individuals with isolated indirect hyperbilirubinemia for vitamin B12



deficiency might permit early diagnosis of this condition. This is important because timely institution of therapy can forestall the development of severe complications such as myelopathy and neuropathy.⁶

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CONFLICTS OF INTEREST

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PATIENT CONSENT

The authors, Sowjanya Dasari, Kushal Naha, Mukhyaprana Prabhu, declare that:

1. They have obtained written, informed consent from the patient for the publication of the details relating to the patient in this report.
2. All possible steps have been taken to safeguard the identity of the patient.
3. This submission is compliant with the requirements of local research ethics committees.