CASE REPORT

Severe unconjugated hyperbilirubinaemia: one and one makes three?

Kushal Naha,¹ Sowjanya Dasari,¹ G Vivek,² Manjunath Hande,¹ Vasudev Acharya¹¹Department of Medicine, Kasturba Medical College, Manipal University, Manipal, Karnataka, India²Department of Cardiology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India

Correspondence to

Dr G Vivek,
vivekgraman@gmail.com

SUMMARY

A 38-year-old housewife presented with a 3-month history of gradually progressive fatigue and deepening jaundice as well as a history of mild fluctuating jaundice since childhood. General examination revealed an obvious icterus. Systemic examination was normal. Laboratory tests confirmed unconjugated hyperbilirubinaemia. Further evaluation yielded a diagnosis of vitamin B₁₂ deficiency on a background of Gilbert's syndrome.

BACKGROUND

Vitamin B₁₂ deficiency is known to produce unconjugated hyperbilirubinaemia due to the phenomenon of ineffective erythropoiesis. The resulting hyperbilirubinaemia, however, is typically mild and overshadowed by obvious signs of vitamin B₁₂ deficiency such as anaemia and peripheral neuropathy. In the presence of pre-existing conjugation defects such as Gilbert's syndrome, vitamin B₁₂ deficiency can produce gross unconjugated hyperbilirubinaemia. This phenomenon is readily demonstrated in this case report.

CASE PRESENTATION

A 38-year-old housewife presented with a 3-month history of progressive fatigue and deepening jaundice for the past 3 months. Jaundice was restricted to her eyes and there was no discolouration of her urine. There were no associated symptoms of haematuria, fever or abdominal pain, and no history of paraesthesia or weakness in her lower limbs. She denied any history of substance abuse. She also reported a history of fluctuating jaundice since childhood, typically of mild intensity and not associated with any systemic symptoms. She could not recollect any precipitating or relieving factors. She consumed a strictly vegetarian diet due to religious reasons.

General physical examination confirmed obvious jaundice involving both scleras. Pallor was absent. Systemic examination was entirely normal. Hepatosplenomegaly was absent. There was no clinical evidence of peripheral neuropathy.

INVESTIGATIONS

Routine laboratory tests showed severe unconjugated hyperbilirubinaemia (total bilirubin: 193.2 µmol/L, conjugated bilirubin: 6.8 µmol/L). Liver function tests were otherwise normal (aspartate aminotransferase: 50 U/L, alanine aminotransferase: 39 U/L, alkaline phosphatase: 69 U/L, albumin: 47 g/L). Blood glucose, renal function tests and serum electrolytes were within normal limits. Serum lactate dehydrogenase (LDH) level was raised (456 U/L; normal

range: 150–250 U/L). Complete blood counts including reticulocyte count were normal (haemoglobin: 125 g/L, total leucocyte count: 7.5×10^9 cells/L, platelet count: 276×10^9 cells/L, reticulocyte count: 2.3%). Red cell indices revealed an elevated mean corpuscular volume (102.7 fL). Peripheral blood smear showed predominantly normochromic normocytic erythrocytes with occasional macrocytes. Bone marrow aspiration and biopsy also yielded features of early megaloblastosis. Serum vitamin B₁₂ levels were assayed by chemiluminescence method and were marginally low (155 pmol/L; normal range: 162–590 pmol/L). Serum folate levels were normal (23.1 nmol/L; normal range: 12.2–40.8 nmol/L).

Although the reticulocyte count was not elevated, the patient was also screened for other haemolytic disorders. Direct Coomb's test was negative; glucose 6-phosphate dehydrogenase activity and pattern of haemoglobin electrophoresis were both normal.

DIFFERENTIAL DIAGNOSIS

► Unconjugated hyperbilirubinaemia due to vitamin B₁₂ deficiency with ineffective erythropoiesis on a background of Gilbert's syndrome (see below).

TREATMENT

Parenteral vitamin B₁₂ supplementation was administered according to protocol (1000 µg cyanocobalamin intramuscular once daily for 1 week, then weekly for 3 weeks and then monthly indefinitely). Gastroscopy for mucosal biopsy was refused by the patient.

OUTCOME AND FOLLOW-UP

On follow-up, the patient reported progressive resolution of jaundice, and serial unconjugated bilirubin levels had stabilised at 47.9 µmol/L by the end of 1 month of therapy. The patient was then reassessed for Gilbert's syndrome. Unconjugated bilirubin level rose to 78.7 µmol/L after 48 h of lipid-free diet, and was then suppressed to 20.5 µmol/L after administration of a single dose of phenobarbitone (100 mg orally) confirming a diagnosis of underlying Gilbert's syndrome. The patient was reassured regarding the benign nature of the disorder.

DISCUSSION

Unconjugated hyperbilirubinaemia is one manifestation of a number of diverse conditions including disorders of bilirubin metabolism such as Gilbert's syndrome, and haemolytic anaemias such as

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hereditary spherocytosis and elliptocytosis associated with excessive generation of unconjugated bilirubin.

Gilbert's syndrome is a benign, familial condition resulting from reduced bilirubin conjugation due to decreased function of the uridine diphosphate glucuronosyltransferase enzyme. It is diagnosed by the estimation of hyperbilirubinaemia after suppression with phenobarbitone and after caloric¹ or lipid restriction.² Genetic testing is also available for Gilbert's syndrome,² although the cost of the test and the benign nature of this disorder limit its application.

In contrast, evidence of haemolysis in the form of elevated serum LDH, reticulocytosis and undetectable serum haptoglobin levels is easier to identify and thus constitutes the first diagnostic step in patients with unconjugated hyperbilirubinaemia. Importantly, patients with compensated haemolysis may not exhibit anaemia. In addition to these well-characterised aetiologies, vitamin B₁₂ deficiency is also known to produce reversible unconjugated hyperbilirubinaemia due to the phenomenon of ineffective erythropoiesis.³ This process involves the lysis of immature erythrocytes within the bone marrow itself, generating excess biliverdin, and ultimately increasing unconjugated bilirubin. The absence of associated reticulocytosis is an important clue to differentiate vitamin B₁₂ deficiency from true haemolytic anaemia. Low serum vitamin B₁₂ levels are obviously confirmatory.

Vitamin B₁₂ deficiency can also manifest with unconjugated hyperbilirubinaemia alone in the absence of anaemia or neurological features; Dasari *et al*⁴ reported this in a patient without Gilbert's syndrome. As the case illustrated, isolated vitamin B₁₂ deficiency is typically associated with only mild unconjugated hyperbilirubinaemia in the presence of intact bilirubin metabolism.

Conversely, pre-existing defects in bilirubin conjugation, chiefly Gilbert's syndrome, can magnify other causes of unconjugated hyperbilirubinaemia, producing overt jaundice. This was demonstrated in a report by Singh and Agarwal⁵ describing a patient with coexistent Gilbert's syndrome and thalassaemia trait with disproportionately elevated unconjugated bilirubin. Similar cases have also been described involving Gilbert's syndrome concomitantly with hereditary spherocytosis^{6–9} and glucose-6-phosphate dehydrogenase deficiency.¹⁰

To the best of our knowledge, however, such a phenomenon has never been described with vitamin B₁₂ deficiency. Nevertheless, the underlying mechanism of disproportionate unconjugated hyperbilirubinaemia appears to be common to the analogous cases mentioned above. The synergistic impact of vitamin B₁₂ deficiency and Gilbert's syndrome in this case, on bilirubin metabolism, supports the contention that one and one can indeed sometimes make three!

Learning points

- ▶ Severe unconjugated hyperbilirubinaemia is very unusual in adults, and mandates a careful search for multiple concomitant aetiologies.
- ▶ Vitamin B₁₂ deficiency is an under-recognised cause for unconjugated hyperbilirubinaemia due to the phenomenon of ineffective erythropoiesis.
- ▶ Two relatively minor clinical manifestations can synergistically produce surprisingly prominent symptoms and signs.

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Competing interests None.

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