Gilbert's syndrome: a short review

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Abstract

Gilbert's syndrome is the most common anomaly of bilirubin transport. The controversy around it is due to the concentration of serial bilirubin in the general population. The authors refer to the need of reassuring patients regarding the benign and inconsequential nature of the disorder and the excellent prognosis.

Key words: jaundice, bilirubin metabolism, caloric restriction.

Introduction

Jaundice is a clinical sign characterized by yellowish coloration of the skin and mucosa, attributed to an increase (higher than 2.5-3,0 mg/dL or 40-50 mmol/L) in plasma bilirubin concentration, which is normally around 0.2-0.8 mg/dL (2.0-17 mmol/L).

The daily production of bilirubin is approximately 200-400 mg; 75% comes from the break down of the erythrocytes in the spleen, liver and bone marrow, 22% from free haem and hepatic catabolism, and 3% from ineffective erythropoiesis.

The total bilirubin fractionation in the conjugated (direct) and unconjugated (indirect) forms, by van den Bergh's diazo reaction is frequently carried out, to distinguish between the two types of hyperbilirubinemia; however, if the total bilirubin does not exceed 5 mg/dL (85 mmol/l) it is not technically possible to separate the two fractions precisely. This problem was overcome with the use of high performance liquid chromatography (HPLC alkaline methanolysis) which demonstrated, through transmethylation of esters, that the conjugated fraction consisted of a mixture of hydrosoluble esters (unlike the non-conjugated fraction), and that part of these bind to the proteins (bili-albumin and biliprotein), representing a significant percentage of the total bilirubinaemia. The percentages of unconjugated fraction of esterified bilirubin and total bilirubin determine the three fundamental alterations to the metabolism of that pigment.[1]

Free unconjugated bilirubin is potentially toxic, particularly for the brain (kernicterus in newborn infants). Normally, this toxicity is prevented by physiological mechanisms that include binding to plasma carrier proteins (albumin), liver capture, conjugation with glucuronic acid, and excretion, through the bile ducts, in the form of bile. In normal situations, the unconjugated fraction represents not more than 1% of the pigments excreted in the bile.

The conjugation of bilirubin is catalyzed by specific isoenzymes, collectively known as uridine-diphosphoglucuronic glucuronosyltransferase (UGT).

Gilbert's syndrome is manifested as intermittent, chronic and benign jaundice, generally detected in adolescence or in early adult age, the objective examination revealing no other signs of chronic hepatic disease. In 50% of cases, it is associated with fatigue, dizziness and migraines, abdominal comfort (with acute pain in rare cases), nauseas and anorexia, diarrhoea or constipation.

It affects around 6% of the general population, with an incidence four times higher in males (in whom the bilirubinaemia is around 0.2-0.3 mg/dL – 3-4 mmol/L higher than in females); [2] it is inherited in 50% of cases, with low-penetrance autosomal dominant transmission.

As the most common disturbance in the transport of bilirubin in the hepatocyte, the study of this syndrome, described for the first time 1901, by Gilbert and Lereboullet, conferred heterogeneity on its pathogenesis.

Three variants are known, sometimes mixed,

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relating to capture (decreased liver clearance of bilirubin by 30% by protein deficit of the membrane) conjugation (partial glucuronyl transferase deficit) and haemolysis.

Berk et al. In studies on clearance of indocyanine green, bromsulphthalein, rifampicin and nicotinic acid, observed that these substances compete with the bilirubin for the same enzymes in the capture process, although they are not glucoronoconjugated, and concluded that in Gilbert's syndrome, there is a quantitative and/or qualitative deficit of these enzymes.

The disturbance in conjugation process, due to the decreased activity of glucuronyl transferase, is the most widely-accepted pathogenic factor, sustained by direct enzyme dosing in the hepatic tissue, and by the response obtained to phenobarbital (enzyme inductor). Black and Billing[3] showed, in 1969, that the enzyme responsible for the hepatic conjugation of bilirubin – UDP glucuronyltransferase – was present in low concentrations in the liver of individuals with Gilbert's syndrome. Unlike estrogens, testosterone[2] decreases the activity of the UDP glucuronyltransferase.

Finally, a possible increase in bilirubin by haemolysis should also be considered, with a slight decrease in the half-life of the erythrocytes,[4] since Gilbert's syndrome is associated with hereditary spherocytosis, glucose-6-phoshate dehydrogenase deficiency and non-spherocytic hemolytic anemia.

In the absence of symptomatic effects on the daily or hourly physiological fluctuations of bilirubin, factors that induce its increase (calorie privation, fasting, physical exercise, stress, infections, alcohol consumption) in predisposed individuals can lead to the appearance of jaundice.

In 1988, Olson et al.[5] classified Gilbert's syndrome as a variant of the normal, in which the population in question had higher bilirubinaemia than the general population.

The diagnosis is generally by exclusion, and it is always suspected that an individual will present unconjugated hyperbilirubinemia (less than 4 mg%), with normal hepatic tests; the histological result of the hepatic biopsy (which should only be carried out when chronic hepatic disease cannot be ruled out by clinical and laboratory tests) is normal or presents non-characteristic alterations: Lipofuscin-like pigment in the centrilobular vein (MO) or hypertrophy of the smooth endoplasmic reticulum (ME).

In practice, a range of readily-accessible diagnostic tests is used, the most common ones being the fasting test (the effect of which is attributed to the removal of lipids in the diet)[6] and the Phenobarbital test, the latter having the advantage that it is less inconvenient for the patient.

Thus, an increase in bilirubin is observed with: 1 – the fasting test: Diet with 400 cal/day ("100g glucose/ 2 liters of water) for 48 hours; 12-24 hours after the reintroduction of a free diet, the values tend to the base level; 2 – nicotinic acid: 3 hours after intravenous administration of 50 mg; 3 – rifampicin: Administer 900 mg p.o. with serum determinations 1,2,3 and 4 hours after the dose; (the first three tests are not free from false-negative results).

Thus, an increase in bilirubin is observed with: phenobarbital (50 mg p.o. 8/8 hours for 3 days) and glutethimide (not sold in Portugal).

The differential diagnosis is made with other hereditary unconjugated hyperbilirubinemia, particularly Crigler-Najjar syndrome (type II), in which a conjugation enzyme deficiency is equally patent, but with greater severity, the non-conjugated fraction being quantified at values under 20 mg% (above this value for type I). The hereditary character is autosomal recessive (for type II) and responds well to phenobarbital.

The noble act of therapy consists of verbally calming the patient. For those in whom jaundice of the sclera is a source of suffering, phenobarbital can be prescribed (100 mg at night).

A review was carried out of five cases, diagnosed in an external Gastroenterology clinic over a one--year period. The population consisted of 4 men and 1 woman, with an average age of 40 years and an age range of 19-53 years.

The motive of the consultation was to investigate asymptomatic hyperbilirubinemia, associated, in four cases, with jaundice of the sclera.

While there was no epidemiology suggestive of viral hepatitis, or regular ingestion of drugs; 3 male patients consumed more than 100g/day of alcohol.

The patients did not show any signs of chronic liver disease, or other physical signs, besides jaundice of the sclera.

The mean total and indirect bilirubin values were 2.7 mg/dL (2.3-3.6) and 2.03 mg/dL (1.4-3.2), respectively.

The remaining hepatic tests were within the normal range, and serological markers of hepatitis A, B and C were negative. The differential reticulocyte count and Coombs direct and indirect test ruled out the association of haemolysis in all cases. Abdominal echography ruled out the existence of lithiasic pathology of the vesicle and main bile duct, as well as focal lesions and/alterations in the echostructure of the hepatic parenchyma.

The diagnosis was based on the clinical and laboratory values, and was confirmed by the calorie restriction test. In 5 patients, an increase in 1.4 mg/dL was observed in non-conjugated bilirubin values, with a decrease in base levels 24 hours after restarting a free diet.

Comments

Gilbert's syndrome is defined as a non-conjugated, benign, hereditary and moderate hyperbilirubinaemia, chronic or recurrent, ruling out the existence of haemolysis (decrease in hemoglobin or increase in reticulocytes) and alterations in the remaining hepatic tests, occurring in the presence of normal hepatic histology, which is not necessary to confirm the diagnosis.

The main difficulty in its diagnosis is the determination of serum bilirubin values considered normal, a question that has been a point of disagreement.[7] This fact is due to the asymmetrical distribution present in the study of various population groups.[5] Another issue relates to the existence or absence of symptoms associated with hyperbilirubinemia, and corresponding degree of the jaundice.[5] For Gollan and Schmidt, those are related to the level of anxiety developed, and not to the underlying pathology. According to Olsson et al., this entity would not need attention if the bilirubinaemia levels did not take on a clinical manifestation; jaundice of the sclera.

It is therefore essential to demystify the "disease" to the patient, and treat it, for cosmetic purposes.

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