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Gilbert's syndrome in identical twins with symptoms in only one twin

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Abstract

Gilbert's syndrome is an inherited disease which presents with unconjugated hyperbilirubinemia caused by decreased uridine diphosphate (UDP) glucuronosyltransferase activity. There are usually no signs or symptoms other than hyperbilirubinemia, especially during stress, but fatigue is not uncommon. It can be confirmed using molecular diagnostics to confirm 7 TA repetitions in the UDP-glucuronosyltransferase, family 1, member 1A (UGT1A1) gene. The case of a young female patient with a twin sister is presented, where one twin sister had symptoms which eventually lead to the diagnosis of Gilbert's syndrome, while the other twin sister did not. Although a speculative conclusion, scholastic achievement and physical activity may be protective for patients with Gilbert's syndrome. In any case, this case report is an example of the importance of thorough propaedeutics, with a focus on taking family history and referring to medical documentation.

Keywords

gilbert's syndrome; identical twins; hyperbilirubinemia

Introduction

Gilbert's syndrome, also known as hyperbilirubinemia 1, is an autosomal recessive inherited disease characterised by chronic non-hemolytic unconjugated hyperbilirubinemia causing decreased activity of liver bilirubin uridine diphosphate (UDP) glucuronosyltransferase (about 30 % from the wild type), which is required for the conjugation and subsequent elimination of bilirubin from the body [1,2]. In Europe, the incidence is about 11-19 % of the total population [3].

Due to non-specific symptoms, most cases are not diagnosed until adolescence [4], possibly due to competitive inhibition of bilirubin conjugation by endogenic steroids which are on the rise during puberty [5]. Symptoms include transient hyperbilirubinemia, jaundice, and changes in drug-metabolism, such as reduced metabolism of acetaminophen, increasing its bioactivation [6]. Other symptoms may be weakness and fatigue, one study describes chronic fatigue syndrome (CFS) [7], abdominal discomfort, nausea, and diarrhea [8]. Symptoms are exacerbated under stress, fatigue, during dehydration, fasting, infection, alcohol consumption, and in the cold [9]. The condition is considered benign with a normal life expectancy, and treatment is generally not required, it is recommended to observe a healthy diet and avoid stress [9].

The TATA box for binding transcription factor II D (TFIID) is found within the promotor region of the UDP-glucuronosyltransferase, family 1, member 1A (UGT1A1) gene, when a mutation is present in this region, specifically when the TATA box is longer, the accuracy and frequency of transcription initiation is reduced, which leads to the reduced expression of the reporter gene, and as a result, serum bilirubin becomes elevated [2]. Up to 6 TA repetitions can be normally found in the gene, 7 TA repetitions is considered confirmation of Gilbert's syndrome [2]. The syndrome can be diagnosed after a thorough interview and physical examination, and confirmed with molecular diagnostics using DNA from a blood sample and the PCR method to test TA repetitions in the UGT1A1 gene (allele *28 [TA6/7]) [10]. Results can show heterozygote or homozygote genotypes, heterozygotes may exhibit slight hyperbilirubinemia, but only homozygotes are confirmed as having Gilbert's syndrome [10].

Case Report

A 16-year old girl presented to our general medical practice with symptoms of weakness and fatigue during the past two to three months, without any other symptoms or signs, all functions and habits normal, no known diseases, and no medication or contraceptives. Physical examination was insignificant. The patient has an identical twin sister who did not have any complaints. Laboratory test results revealed possible signs of megaloblastic anaemia (slightly macrocytic, hyperchromic erythrocytes, HCT 0.400 L/L (0.354 – 0.450), erythrocytes 4.34 x 10^{12}/L (4.07 - 5.42), Hgb 141 g/L (118 - 149), MCV 92.2 fL (76.5 - 92.1), MCH 32.5 pg (24.3 - 31.5), MCHC 352 g/L (304 - 346)) and hyperbilirubinemia (33 µmol/L (Ref. 6 - 26)). Pernicious and hemolytic anaemia were possible considering the erythrocyte status and hyperbulirubinemia, but since anaemia was not pronounced, taking into consideration the age and symptoms, Gilbert's syndrome was a highly likely diagnosis. Additional tests were ordered, vitamin B12 levels, which were normal (378 pmol/L (138-652)) and excluded pernicious anaemia, as well as total, conjugated, and unconjugated bilirubin (respectively 48 umol/L, 8 umol/L, 40 umol/L (6 - 26)), showing elevated unconjugated bilirubin, which did not exclude hemolytic anaemia, nor Gilbert's syndrome. Looking at laboratory test results retroactively, bilirubin was not tested in the patient before, but also looking at results from her twin sister, keeping in mind Gilbert's syndrome is genetic, one slightly elevated result was found (28 µmol/L (6 – 26)) from two years earlier. At this point, considering everything, Gilbert's syndrome seemed most probable, molecular diagnostics was ordered for both, and the diagnosis of Gilbert's syndrome was subsequently confirmed with 7 TA repetitions in both twin sisters.

A follow up interview with the patient about her and her twin sister was performed with parental and patient's consent to gain insight into how one twin sister presented with symptoms and hyperbilirubnemia, while the other did not. The twin sisters live in a small town with their parents, and a few other family members, they have a dog, more or less the same friends, no romantic partners, attend the same school, and have similar interests. They are both good students, and partake in archery and orchestra, the twin sister also practices karate. They do not have any part time jobs. Eating habits are more or less the same, breakfast, lunch, and dinner. The patient notes she enjoys going out with friends more, while her twin sister likes to stay in more and study, currently she is preparing for a scholastic competition. The patient explains she might be more easily stressed than her sister, but no other significant differences were described or noted.

Discussion

This case report certainly does not present any ground-breaking discoveries, but it is a classic case of nature versus nurture, where the nature, or in this case genetics, is identical, and the nurture, or environment and circumstances are more or less the same also except for a couple of minor details. To our knowledge, there are not many case reports of Gilbert's syndrome in twins, and it is hoped that this classic comparison might spark some novel insight, idea, or motivation for Gilbert's syndrome. It is unclear why the patient presented with symptoms of Gilbert's syndrome while her twin sister did not, considering the similar surroundings. The only notable differences are the patient is slightly more socially inclined and possibly easily stressed, while her identical twin sister is more academically inclined and additionally practices karate. Perhaps scholastic achievement and physical activity have a protective effect for patients with Gilbert's syndrome, admittedly, this report does not prove this, but it also does not disprove it. This is only speculation at best, but as with any form of scientific work, it might lead to further advances. In any case, a confirmed diagnosis of Gilbert's syndrome is important to avoid unnecessary testing when hyperbilirubinemia is discovered, and serves as a good of example of the importance of diagnosing abnormal results for future reference. This case also reiterates the importance of taking diligent notes as a part of a patient's record for future reference, as well as the importance of obtaining family anamnesis, as shown by looking at previous laboratory results and comparing siblings, albeit identical, which helped make the final diagnosis of Gilbert's syndrome with less effort, and only a handful of tests. Today's doctors with a primarily curative approach to medicine, focusing on the present status of a patient, due to lack of time and abundant administration, may be forgetting the importance of thorough propaedeutics.

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