

**BEUTLER, Katarzyna and LEWANDOWSKI, Jędrzej. Gilbert's syndrome - bright and dark sides of the disease - literature review. Journal of Education, Health and Sport. 2024;63:146-154. eISSN 2391-8306. <https://dx.doi.org/10.12775/JEHS.2024.63.011>
<https://apcz.umk.pl/JEHS/article/view/48507>
<https://zenodo.org/records/10700780>**

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences). Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). © The Authors 2024; This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland
Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 02.02.2024. Revised: 15.02.2024. Accepted: 23.02.2024. Published: 24.02.2024.

Gilbert's syndrome - bright and dark sides of the disease - literature review

Katarzyna Beutler

University Clinical Hospital of Poznan, Długa 1/2, 61-848 Poznan

kasia.beutler@gmail.com

<https://orcid.org/0009-0000-4219-5676>

Jędrzej Lewandowski

University Clinical Hospital of Poznan, Długa 1/2, 61-848 Poznan

jedrzejlewandowski98@gmail.com

<https://orcid.org/0009-0006-0608-0154>

ABSTRACT

Gilbert's syndrome is the most common inherited jaundice worldwide. It affects 5-10% of the population. It is caused by a mutation of the UGT1A1 gene, which results in impaired bilirubin metabolism. It is a benign disease and does not affect the life expectancy of patients. Patients with Gilbert's syndrome should be alert to factors that exacerbate the course of the disease, interactions with medications taken and possible comorbidities such as hemolytic anemia, cholelithiasis or schizophrenia. However, it is the responsibility of physicians with such patients under their care to properly educate patients. Gilbert's syndrome carries not only the consequences associated with the mutation, but also has many benefits that patients may not be fully aware of. Mildly elevated bilirubin levels have an antioxidant and anti-inflammatory effect, which prevents the development of lifestyle diseases and cancer. Ongoing clinical trials suggest that this could be a great step toward new treatments for diseases affecting the entire human population.

PURPOSE OF THE WORK: This review paper aims to show Gilbert's syndrome as a multifaceted disease and to sensitize doctors' attention to patients with the described mutation.

MATERIALS AND METHODS: An analysis of papers available in PubMed and Google Scholar was performed using the following key words: Gilbert's syndrome, bilirubin, UDP-glucuronosyltransferase, Gilbert's syndrome harmful and protective aspects, iatrogenic Gilbert's syndrome

RESULTS: The result of the work is to present Gilbert's syndrome as a disease that carries medical problems directly related to the mutation, but also, in some cases, has a protective effect on affected individuals. The work highlights the complexity of the problem.

KEYWORDS: Gilbert's syndrome, bilirubin, UDP-glucuronosyltransferase, Gilbert's syndrome harmful and protective aspects, iatrogenic Gilbert's syndrome

1. INTRODUCTION

Gilbert's syndrome is a genetic disorder first described in 1901 by Augustin Gilbert. It is mainly inherited autosomal recessively, but dominant variants also occur.(1-3) In this syndrome, we are dealing with mild and intermittent isolated elevated levels of unconjugated bilirubin. Affected patients present with periodic, painless and non-itching jaundice. Sometimes they may complain of indigestion and pain in the right lower abdomen.(1,3) Gilbert's syndrome may be diagnosed incidentally during routine blood tests, which reveal unconjugated hyperbilirubinemia. Liver parameters and indicators of hemolysis remain normal.

Factors that exacerbate the course of the disease include stress, alcohol, dehydration, heavy exercise, surgery or comorbidities, as well as sleep deprivation or starvation.(1,4) Gilbert's syndrome is a benign disease, and the life expectancy of patients with the syndrome is the same as that of healthy adults. Interestingly, the mildly elevated levels of free bilirubin present in Gilbert's syndrome may have a protective effect against many diseases such as cardiovascular disease, type 2 diabetes, as well as cancer. Research is currently underway toward the use of bilirubin administration as a new drug.(1,5–7)

This review paper aims to show Gilbert's syndrome as a disease with which it is possible to live a completely normal life, and to reap the health benefits that result from the described mutation.

2. EPIDEMIOLOGY

Gilbert's syndrome is the most common cause of inherited jaundice in the world.(1,6) It occurs in about 5-10% of people in the general population, mostly in young adults. Men are more often affected.(3,8,9) In Caucasians, the frequency of mutant alleles is higher.(1)

3. PATHOMECHANISM

Bilirubin is a breakdown product of heme present in the human body in hemoglobin, many enzymes and myoglobin. Under physiological conditions, heme is degraded by heme oxidase 1, where biliverdin is formed, among other things. Biliverdin is then converted to unconjugated bilirubin by the action of biliverdin reductase. It is a water-insoluble product. Albumin binds unconjugated bilirubin and transports it to the liver, where the process of conjugation with glucuronic acid takes place with the participation of the enzyme UDP-glucuronosyltransferase. It results in the formation of conjugated bilirubin, which is then excreted with bile. The enzyme UDP-glucuronosyltransferase is encoded in the UGT1A1 gene.(1,6,10)

In Gilbert's syndrome, there is a mutation that results in a malfunction of the enzyme UDP-glucuronosyltransferase. This enzyme works more slowly and less efficiently than in a healthy person. The result is a periodic increase in the level of unconjugated bilirubin in the body. The most common mutation occurs in the TATA sequence of the UGT1A1 gene promoter. An additional TA sequence is added to the proximal promoter field. The mutation is called UG1A1*28 mutation. The activity of the enzyme UDP-glucuronosyltransferase is then about 30% of the enzyme activity in healthy individuals.(6,8,11–14) There are also cases where mutations occur in exons of the UGT1A1 gene. This type of mutation is prevalent in Asians.(1,6,14)

4. DIAGNOSTICS AND TREATMENT

The diagnosis of Gilbert's syndrome is a diagnosis by exclusion in individuals with elevated levels of unconjugated bilirubin and normal liver enzymes.(2,8,15) The doctor should always take a detailed history with the patient with special emphasis on medications taken, alcohol abuse and family history, examine the patient physically and order laboratory and imaging tests.(16) Hematologic disorders, Crigler-Najjar syndrome, Rotor syndrome, Dubin-Johnson syndrome and liver diseases that may cause a similar clinical picture should be excluded.(9) The normal range for unconjugated bilirubin in adults is 0.2-1.2 mg/dl, while Gilbert's syndrome patients usually have unconjugated bilirubin levels of no more than 4-5 mg/dl.(16) In uncertain cases and to rule out other genetic diseases associated with the UGT1A1 mutation, a genetic test can be performed. The disease does not lead to liver damage.(17) Patients with Gilbert's syndrome do not require treatment or adherence to restrictive diets.(2,8) However, a case is described where a patient suffering from Gilbert's syndrome with associated symptoms in the form of migraine, granulomatous dermatitis and fatigue saw improvement after being put on a ketogenic paleolithic diet.(18)

5. HARMFUL EFFECTS

Homozygotes for the promoter variant of the UGT1A1*28 gene have an increased risk of developing gallstones.(4,8,17) As a result of conjugation disorders caused by the mutation, bilirubin monoglucuronide is excreted along with bile. It is less soluble in water, which is a risk factor for the formation of gallstones.(19) Also, the use of drugs by such individuals that require glucuronidation, in which UGT1A1 is involved, increases the risk of side effects of these drugs.(4) An example of such a drug is irinotecan, used to treat metastatic colorectal cancer, which can cause myelosuppression and diarrhea as a result of ineffective glucuronidation. The described side effects occur in 25% of those treated. Another drug is atazanavir, which, by blocking UG1A1, can further exacerbate hyperbilirubinemia and thus cause jaundice.(2,8,10,20) In addition, an increased risk of colorectal cancer and breast cancer has been observed in patients with Gilbert's syndrome.(17) There is an association between Gilbert's syndrome and the occurrence of hemolytic anemia. It has been observed to affect up to 50% of patients. (9,13,21). The enzyme UDP-glucuronosyltransferase is involved in the metabolism of estrogens. Mutation of the gene encoding this enzyme results in their slower glucuronidation and thus an increase in the concentration of estrogens in the body, which is a risk factor for breast cancer.(10) In addition, patients with Gilbert's syndrome are significantly more likely to have schizophrenia. The exact pathomechanism and correlation with elevated bilirubin levels in patients with schizophrenia is under investigation.(22)

6. PROTECTIVE ACTIVITY

Elevated bilirubin levels have anti-inflammatory and antioxidant effects. Even small, micromolar changes in serum bilirubin levels are associated with significant changes in the risk of various diseases of civilization.(23) People with Gilbert's syndrome are noted to have reduced levels of oxidative stress markers, which correlates with a low incidence of ischemic heart disease.(2,4,24,25) Bilirubin has an inhibitory effect on lipid peroxidation, which protects against atherogenesis.(26) A study was conducted where patients with Gilbert's syndrome were shown to have a significantly lower risk of cardiovascular disease, as well as higher blood levels of HDL cholesterol.(27) The described risk is lower up to 80% compared to healthy people.(26) Additionally, patients with Gilbert's syndrome have a lower risk of developing endometrial cancer and have better overall survival for Hodgkin's lymphoma.(2,8,17,28) It is thought that bilirubin may have antiproliferative properties, reducing the risk of metaplasia and new cancer cell formation in these patients.(27) A 10-year follow-up of men and women was carried out and it was observed that in groups where blood bilirubin levels in the subjects were elevated, the risk of death from cancer was lower than in control groups.(10) In addition, patients have a lower BMI and less tendency to gain weight later in life.(7,16,29,30) With elevated blood bilirubin levels, the body's sensitivity to insulin increases, which is associated with a reduced risk of type 2 diabetes and metabolic syndrome.(16) Clinical studies have also highlighted the immunosuppressive effect of bilirubin, which has an inhibitory effect on the development of immune diseases.(6)

7. IATROGENIC GILBERT'S SYNDROME

Based on the latest scientific evidence and clinical studies, iatrogenic induction of Gilbert's syndrome is being considered for the prevention of civilization diseases.(16) Bilirubin nanoparticles are experimentally administered intraperitoneally and intravenously to achieve mild hyperbilirubinemia. Pegylated bilirubin has been used to treat pneumonia and colitis, leading to bilirubin concentrations in the body characteristic of Gilbert's syndrome. Antitumor effects have also been observed following the administration of biotinylated bilirubin nanoparticles. It now appears that modulation of bilirubin homeostasis at both the systemic and tissue levels is an effective method of preventing many diseases associated with inflammation and oxidative stress. There is great therapeutic potential for bilirubin-based approaches.(6) Another possibility is also partial inhibition of UGT1A1, which will inhibit bilirubin coupling and increase bilirubin concentration. However, further research is needed to fully discover a new treatment.(16)

8. CONCLUSIONS

Gilbert's syndrome is a genetically inherited disease associated with mutation of the UGT1A1 gene promoter. On the one hand, when dealing with patients suffering from this syndrome, one should always take into account the possibility of more frequent comorbidities such as gallstones, hemolytic anemia, or schizophrenia, as well as the possibility of hypersensitivity to certain drugs. It is important to surround the patient with proper medical care and adequate education about the disease. On the other hand, mild hyperbilirubinemia protects patients with Gilbert's syndrome from diseases that affect most of the population on a daily basis. These include lifestyle diseases such as cardiovascular disease or type 2 diabetes and cancer. This knowledge and further investigation of the relationship between slightly elevated bilirubin levels and its protective effect could have a significant impact on the development of treatments for the aforementioned diseases in the future. The use of bilirubin administration as a new drug is very promising; however, it still requires further research.

DISCLOSURE

Author's contribution:

Conceptualization: KB

Methodology: KB

Software: JL

Check: JL

Formal Analysis: JL

Investigation: KB

Resources: KB

Data Curation: JL

Writing-Rough Preparation: KB

Writing-Review and Editing: JL

Visualization: KB

Supervision: JL

Project Administration: KB

All authors have read and agreed with the published version of the manuscript.

Funding Statement: The Study Did Not Receive Special Funding.

Institutional Review Board Statement: Not Applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Not Applicable.

Conflict Of Interest: The authors declare no conflict of interest.

REFERENCES

1. King D, Armstrong M. Overview of Gilbert's syndrome. *Drug Ther Bull.* luty 2019;57(2):27–31.
2. Fretzayas A, Moustaki M, Liapi O, Karpathios T. Eponym: Gilbert syndrome. *Eur J Pediatr.* styczeń 2012;171(1):11–5.
3. Erlinger S, Arias IM, Dhumeaux D. Inherited Disorders of Bilirubin Transport and Conjugation: New Insights Into Molecular Mechanisms and Consequences. *Gastroenterology.* czerwiec 2014;146(7):1625–38.
4. Horsfall LJ, Nazareth I, Pereira SP, Petersen I. Gilbert's syndrome and the risk of death: A population-based cohort study. *J Gastroenterol Hepatol.* październik 2013;28(10):1643–7.
5. Wagner KH, Shiels RG, Lang CA, Seyed Khoei N, Bulmer AC. Diagnostic criteria and contributors to Gilbert's syndrome. *Crit Rev Clin Lab Sci.* 17 luty 2018;55(2):129–39.
6. Vitek L, Bellarosa C, Tiribelli C. Induction of Mild Hyperbilirubinemia: Hype or Real Therapeutic Opportunity? *Clin Pharmacol Ther.* wrzesień 2019;106(3):568–75.
7. Zöhrer PA, Hana CA, Seyed Khoei N, Mölzer C, Hörmann-Wallner M, Tosevska A, i in. Gilbert's Syndrome and the Gut Microbiota – Insights From the Case-Control BILIHEALTH Study. *Front Cell Infect Microbiol.* 16 wrzesień 2021;11:701109.
8. Thoguluva Chandrasekar V, Faust TW, John S. Gilbert Syndrome. W: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cytowane 19 styczeń 2024]. Dostępne na: <http://www.ncbi.nlm.nih.gov/books/NBK470200/>
9. Zespół Gilberta – standard diagnostyczno-terapeutyczny - Standardy medyczne [Internet]. [cytowane 20 styczeń 2024]. Zespół Gilberta – standard diagnostyczno-terapeutyczny - Standardy Medyczne. Dostępne na: <https://www.standardy.pl/artykuly/id/1497>
10. Gil J, Sasiadek MM. Gilbert syndrome: the *UGT1A1* *28 promoter polymorphism as a biomarker of multifactorial diseases and drug metabolism. *Biomark Med.* kwiecień 2012;6(2):223–30.
11. Kundur AR, Santhakumar AB, Bulmer AC, Singh I. Mildly elevated unconjugated bilirubin is associated with reduced platelet activation-related thrombogenesis and inflammation in Gilbert's syndrome. *Platelets.* 17 listopad 2017;28(8):779–85.
12. Vitek L, Ostrow J. Bilirubin Chemistry and Metabolism; Harmful and Protective Aspects. *Curr Pharm Des.* 1 wrzesień 2009;15(25):2869–83.
13. Rawa K, Adamowicz-Salach A, Matysiak M, Trzemecka A, Burzynska B. Coexistence of Gilbert syndrome with hereditary haemolytic anaemias. *J Clin Pathol.* lipiec 2012;65(7):663–5.

14. Burchell B, Hume R. Molecular genetic basis of Gilbert's syndrome. *J Gastroenterol Hepatol.* październik 1999;14(10):960–6.
15. De Morais SMF, Uetrecht JP, Wells PG. Decreased glucuronidation and increased bioactivation of acetaminophen in Gilbert's syndrome. *Gastroenterology.* luty 1992;102(2):577–86.
16. Vitek L, Tiribelli C. Gilbert's syndrome revisited. *J Hepatol.* październik 2023;79(4):1049–55.
17. Strassburg CP. Hyperbilirubinemia syndromes (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor syndrome). *Best Pract Res Clin Gastroenterol.* październik 2010;24(5):555–71.
18. Tóth C, Clemens Z. Gilbert's Syndrome Successfully Treated with the Paleolithic Ketogenic Diet. *Am J Med Case Rep.* 9 kwiecień 2015;3(4):117–20.
19. Tsezou A, Tzetis M, Giannatou E, Spanos I, Roma E, Fretzayas A, i in. Gilbert Syndrome as a Predisposing Factor for Cholelithiasis Risk in the Greek Adult Population. *Genet Test Mol Biomark.* luty 2009;13(1):143–6.
20. Li M, Chan WW, Zucker SD. Association Between Atazanavir-Induced Hyperbilirubinemia and Cardiovascular Disease in Patients Infected with HIV. *J Am Heart Assoc.* 6 październik 2020;9(19):e016310.
21. Kang LL, Ma YJ, Zhang HD. Carbon monoxide breath test assessment of mild hemolysis in Gilbert's syndrome. *Medicine (Baltimore).* luty 2020;99(7):e19109.
22. Miyaoka T, Seno H, Itoga M, Iijima M, Inagaki T, Horiguchi J. Schizophrenia-Associated Idiopathic Unconjugated Hyperbilirubinemia (Gilbert's Syndrome). *J Clin Psychiatry.* 15 listopad 2000;61(11):868–71.
23. Vitek L. Bilirubin as a predictor of diseases of civilization. Is it time to establish decision limits for serum bilirubin concentrations? *Arch Biochem Biophys.* wrzesień 2019;672:108062.
24. Wang X, Chowdhury JR, Chowdhury NR. Bilirubin metabolism: Applied physiology. *Curr Paediatr.* luty 2006;16(1):70–4.
25. Bulmer AC, Blanchfield JT, Toth I, Fassett RG, Coombes JS. Improved resistance to serum oxidation in Gilbert's syndrome: A mechanism for cardiovascular protection. *Atherosclerosis.* sierpień 2008;199(2):390–6.
26. Kundur AR, Singh I, Bulmer AC. Bilirubin, platelet activation and heart disease: A missing link to cardiovascular protection in Gilbert's syndrome? *Atherosclerosis.* marzec 2015;239(1):73–84.

27. Schwertner HA, Vitek L. Gilbert syndrome, UGT1A1*28 allele, and cardiovascular disease risk: Possible protective effects and therapeutic applications of bilirubin. *Atherosclerosis*. maj 2008;198(1):1–11.
28. Strassburg CP. Gilbert-Meulengracht's syndrome and pharmacogenetics: is jaundice just the tip of the iceberg? *Drug Metab Rev*. luty 2010;42(1):168–81.
29. Wagner KH, Seyed Khoei N, Hana C, Doberer D, Marculescu R, Bulmer A, i in. Oxidative Stress and Related Biomarkers in Gilbert's Syndrome: A Secondary Analysis of Two Case-Control Studies. *Antioxidants*. 15 wrzesień 2021;10(9):1474.
30. Wallner M, Bulmer AC, Mölzer C, Müllner E, Marculescu R, Doberer D, i in. Haem catabolism: a novel modulator of inflammation in Gilbert's syndrome. *Eur J Clin Invest*. wrzesień 2013;43(9):912–9.