

Asthma and hyperbilirubinemia: a new aspect to analyze?

Eliza Wasilewska¹, Barbara Kaczorowska-Hań^{2,3}, Beata Burzyńska⁴, Sylwia Małgorzewicz⁵, Ewa Jassem¹

¹Department of Allergology, Medical University of Gdańsk, Gdańsk, Poland

²Department of Occupational Therapy, Gdańsk University of Physical Education and Sport, Gdańsk, Poland

³Paediatric, Haematology Department, Medical University of Gdańsk, Gdańsk, Poland

⁴Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland

⁵Department of Clinical Nutrition, Medical University of Gdańsk, Gdańsk, Poland

Adv Dermatol Allergol 2019; XXXVI (5): 639–642

DOI: <https://doi.org/10.5114/ada.2019.89511>

One of the concepts of airway inflammation in asthma is the occurrence of oxidative stress defined as the disruption of the balance between the level of oxidants and reductants (antioxidants). Several factors, such as cigarettes, marijuana smoking, air pollution, stress, improper dietary habits e.g. eating processed food with a high content of preservatives, can increase the severity of oxidative stress. Conversely, bilirubin is considered to be a factor having cytoprotective properties which include antioxidant, anti-inflammatory, and antiproliferative effects [1]. However, its total effect on the pulmonary system remains unknown.

We report the case of a 16-year-old boy, admitted to the Allergology Department due to ongoing 5 h of dyspnea and jaundice. The patient had a history of recurrent bronchitis from 3 to 5 years of age approximately 4 times a year, and less from the age of 6 – 2 times a year, but bronchitis was accompanied by prolonged cough of up to 4 weeks. He has poor tolerance of exercise from the age of 10, and reported symptoms which included coughing, wheezing, dyspnea and fatigue especially after physical exercises and swimming. In addition, he sometimes experiences loss of appetite and had also accidentally noticed jaundice on the same days, when he had coughing and wheezing. The patient's parents attributed the symptoms to intensive studying and examination-related stress, and poor dietary habits as he often ate processed food such as chips and cola. The patient had a history of hyperbilirubinemia (14 mg/dl) at birth, however no further diagnosis had been pursued at the time. Since then, the level of bilirubin has never been marked. The patient had a family history of chronic diseases, negated having alcohol intake, or drug abuse. On physical examination, superficial jaundice, dyspnea, wheezing and pharyngeal erythema were noted. His full blood count values, C protein (1.00 mg/l), reticulocytes

(0.5%), iron concentration (87 µg/dl), transferrin saturation (32%), liver function tests (ALT, AST, gGT) were normal despite unconjugated bilirubin (7.49 mg/dl). Tests for lamblia (stool microscopy and antigen testing), AgHBs and HCV antibodies were negative, abdominal ultrasonography was normal. The pulmonary function test (Spirometer *Jaeger*) revealed: forced expiratory volume in 1 s (FEV₁) 63%, predicted value (PV), forced vital capacity (FVC) 78%, PV, FEV₁/FVC – 68%. The challenge test with 400 µg of salbutamol was positive (ΔFEV₁ – 28.4%, ΔFVC 210 ml). He was intensively treated with nebulization with short-acting β₂ mimetics and steroids (budesonide), with a good effect, shortness of breath, subsided after a few hours. Afterwards, treatment with nebulization was continued and it was noted that dyspnea, wheezing disappeared, presenting jaundice had reduced. Follow-up laboratory tests performed 5 days later showed normal bilirubin concentration (1.1 mg/dl), total IgE level 46.35 kU/l, specific IgE to inhalant allergens undetectable despite cockroach allergen (53.70 kU/l). Skin prick tests (Allergopharma, Germany) were positive only for cockroach allergen. After 3 days of nebulization, the boy was treated with short-acting β₂ mimetics and steroids (ciclesonide 160 mg twice daily) in an inhaled form and oral leukotriene modifiers 10 mg daily. After 3 months his exercise tolerance improved, spirometry values improved, but the challenge test was positive.

Due to the high levels of bilirubin and jaundice, genetic testing for Gilbert's syndrome (GS) was carried out. Genomic DNA was isolated from peripheral blood samples and the patient was found to be homozygous for the UDP-glucuronosyltransferase 1A1 (UGT1A1) promoter mutation characteristic of GS (Figures 1, 2). Owing to the fact that the bilirubin levels were relatively higher than those associated with GS, we also decided to test for HFE mutations and H63D mutation carriage was confirmed (Figures 3, 4).

Address for correspondence: Eliza Wasilewska MD, PhD, Department of Allergology, Medical University of Gdansk, 7 Debinki St, 80-211 Gdańsk, Poland, phone: +48 58 349 27 24, fax: +48 58 349 27 23, e-mail: ewasilewska@gumed.edu.pl

Received: 24.01.2018, **accepted:** 4.06.2018.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0). License (<http://creativecommons.org/licenses/by-nc-sa/4.0/>)

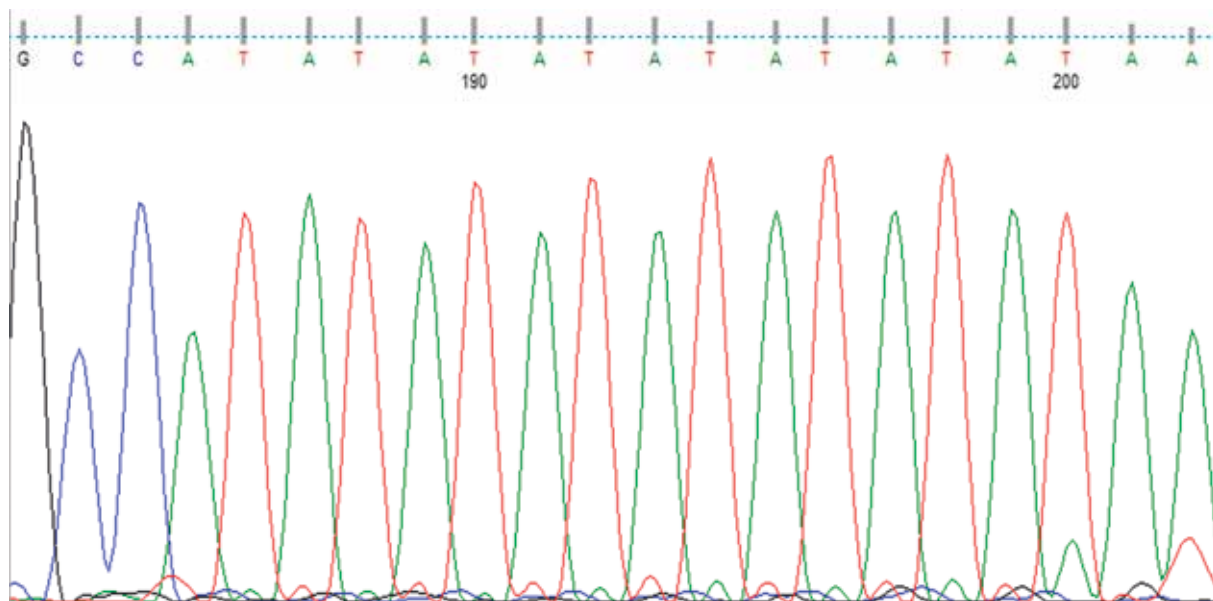


Figure 1. Results of Gilbert's syndrome mutation analysis – patient (TA)7/(TA)7. Genomic DNA was isolated from peripheral blood samples using the MagNA Pure Compact Nucleic Acid Isolation Kit I (Roche, Germany). The promoter region of the UGT1A1 gene was amplified by polymerase chain reaction (PCR) with F primer 5' AAAGTGAACCTCCTGCTACC 3' and R primer 5' TGCTCCTGCCAGAGGTT 3'. Cycling conditions comprised 30 cycles of denaturation at 95° for 30 s, annealing at 52° for 30 s, and extension at 72° for 20 s. The PCR fragments were sequenced directly in both directions with BigDye Terminators and appropriate primers using an ABI Prism 377 sequencer (Applied Biosystems, CA, USA). Sequencing of the promoter region of the UGT1A1 gene revealed a (TA)7/(TA)7 genotype and the patient was found to be homozygous for the UGT1A1 promoter mutation characteristic of Gilbert's syndrome

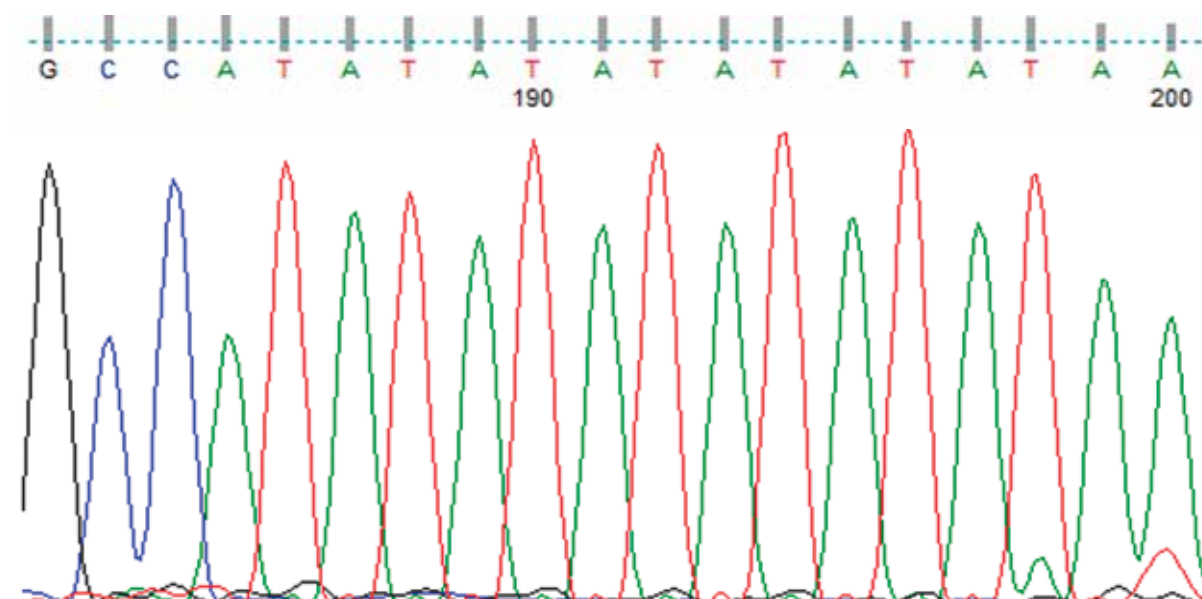


Figure 2. Results of Gilbert's syndrome mutation analysis – healthy control (TA)6/(TA)6

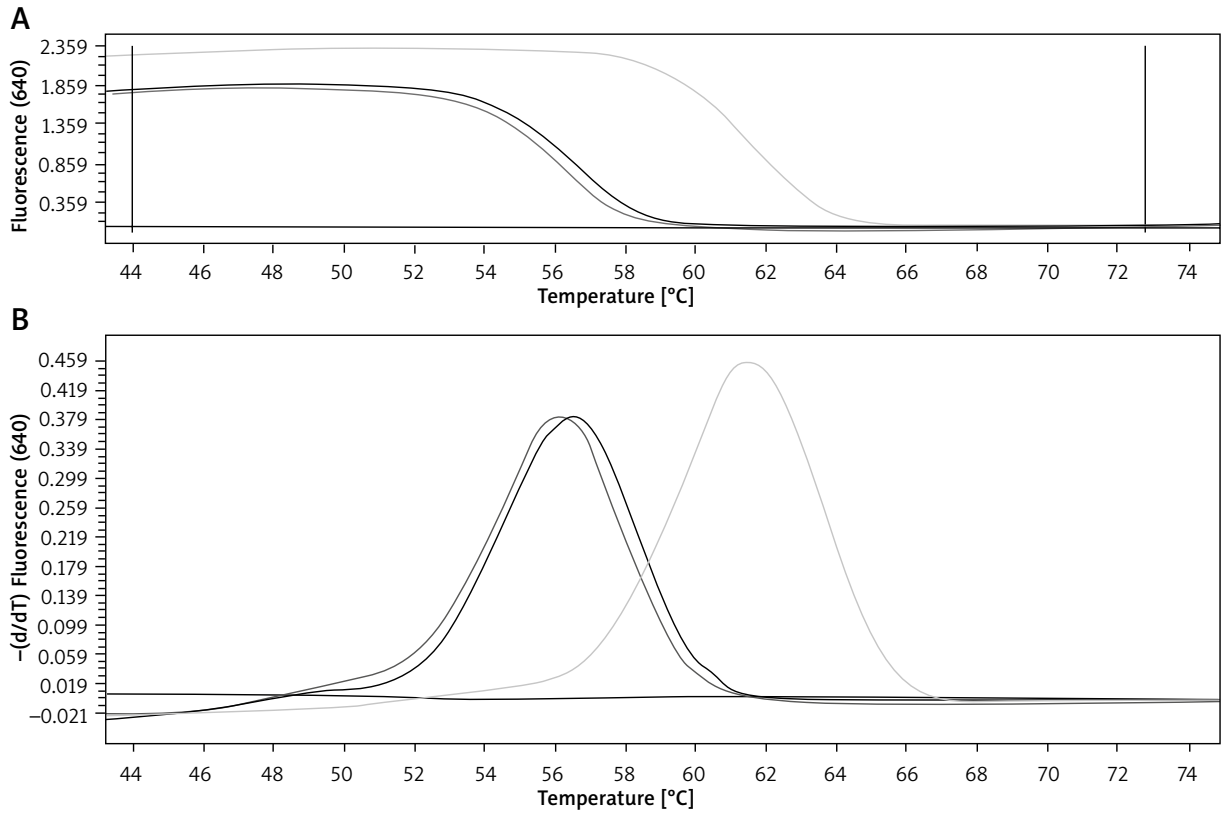


Figure 3. Genotyping of HFE gene mutation – patient with a HFE mutation (A – melting curves, B – melting peaks)

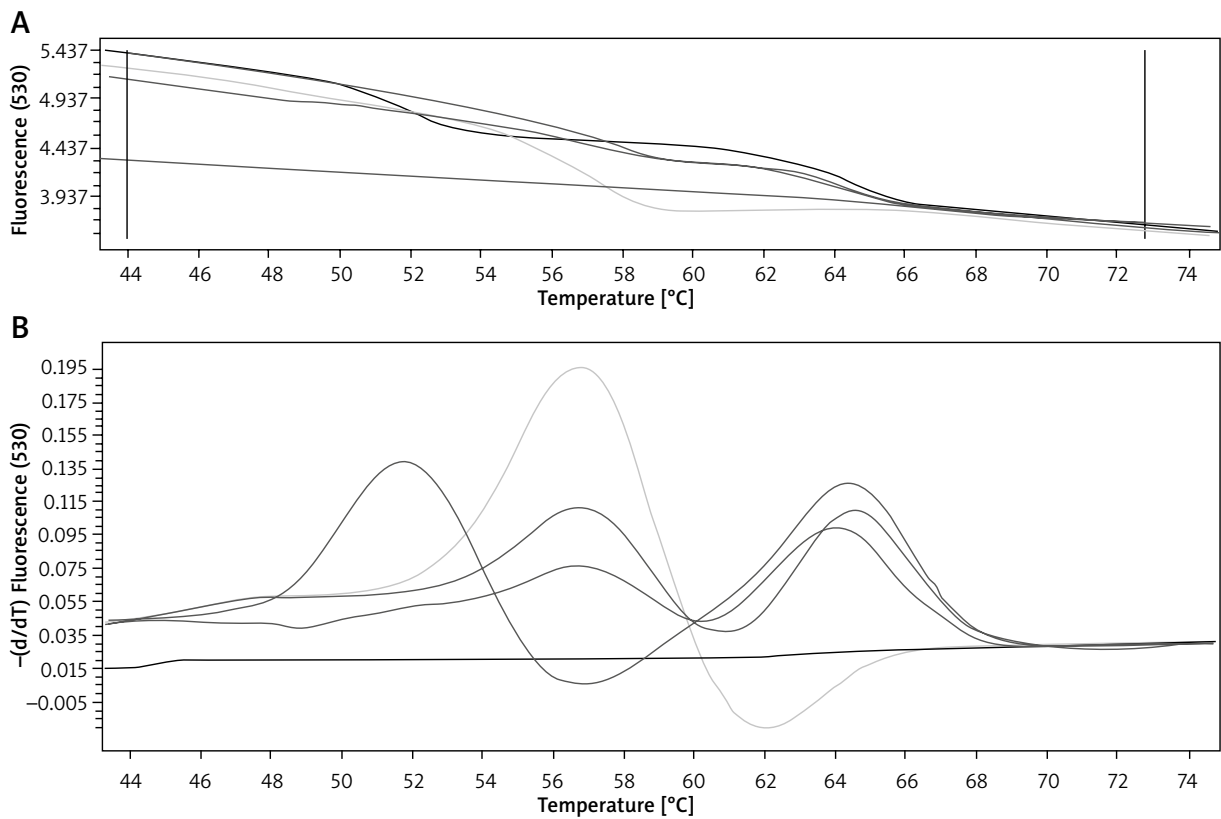


Figure 4. Genotyping of HFE gene mutation – healthy control

Our final diagnosis was uncontrolled asthma, hyper-reactivity to cockroach allergen, Gilbert's syndrome, and carriage of HFE mutation.

To our knowledge this is the first report of a patient with hyperbilirubinemia and asthma exacerbation. Experimental studies using animal models support a protective effect of bilirubin against respiratory injury by environmental factors [2, 3]. A similar positive role of bilirubin on pulmonary function and lower rates of respiratory diseases has been noted in some cohort studies [4, 5]. Horsfall *et al.* concluded that patients predisposed to Gilbert's syndrome have higher pulmonary function (mean FEV₁ and FVC) but the authors took into account only the genetic mutation and not the level of bilirubin in the blood [6]. GS is a genetic disease characterized by mild hyperbilirubinemia, with absence of liver disease or overt hemolysis, UGT1A1 activity < 35% of the normal value, caused by mutations in the UGT1A1 gene which encodes hepatic UGT1A1. GS occurs in 9% of the general population, and as a mild disorder does not require treatment. In another study, the same authors described a correlation between relatively high bilirubin levels within the normal range and a lower risk of COPD and lung cancer [5].

Despite the protective role of bilirubin on pulmonary function, our patient with hyperbilirubinemia presented with asthma. We concluded that coexistence of some other factors, such as stress, improper diet with low antioxidant agents, and exposure to chlorinated swimming pools may cause exacerbation of asthmatic symptoms even if the level of bilirubin is high. Moreover, our patient had high levels of bilirubin at birth and some studies have found a link between neonatal hyperbilirubinemia and childhood asthma and allergic diseases [7]. In addition, we do not know the effects of HFE mutations on hyperbilirubinemia and asthma. Mutation of HFE genes which are responsible for iron metabolism, leads to increased intestinal iron absorption which results in iron overload and, consequently, hemochromatosis (HH). HFE-related hemochromatosis is the most frequent form of the disease and the most common autosomal recessive disorder in Northern European populations, with a prevalence of 1 : 200 to 1 : 250 for homozygosity and a carrier rate of 1 : 8 to 1 : 12. The symptomatic phenotype preceded by fatigue, arthropathy and impotence, occurs in homozygotic males predominantly between the 4th and 6th decade of life, depending on gene penetration and multiple concomitant factors [8]. The clinical impact of HFE gene carriage is still unknown.

In conclusion, the authors suggest a need for further research to examine whether the hyperbilirubinemia (e.g. Gilbert syndrome and/or hemochromatosis) has a protective or toxic effect on pulmonary function (in particular the effect on airway inflammation in asthma).

Conflict of interest

The authors declare no conflict of interest.

References

1. Nakagami T, Toyomura K, Kinoshita T, Morisawa S. A beneficial role of bile pigments as an endogenous tissue protector: anti-complement effects of biliverdin and conjugated bilirubin. *Biochim Biophys Acta* 1993; 1158: 189-93.
2. Wang HD, Yamaya M, Okinaga S, et al. Bilirubin ameliorates bleomycin-induced pulmonary fibrosis in rats. *Am J Respir Crit Care Med* 2002; 165: 406-11.
3. McCarty MF. "Iatrogenic Gilbert syndrome" – a strategy for reducing vascular and cancer risk by increasing plasma unconjugated bilirubin. *Med Hypotheses* 2007; 69: 974-94.
4. Curjuric I, Imboden M, Adam M, et al. Serum bilirubin is associated with lung function in a Swiss general population sample. *Eur Respir J* 2014; 43: 1278-88.
5. Horsfall LJ, Rait G, Walters K, et al. Serum bilirubin and risk of respiratory disease and death. *JAMA* 2011; 305: 691-7.
6. Horsfall LJ, Hardy R, Wong A, et al. Genetic variation underlying common hereditary hyperbilirubinaemia (Gilbert's syndrome) and respiratory health in the 1946 British birth cohort. *J Hepatol* 2014; 61: 1344-51.
7. Huang L, Bao Y, Xu Z, et al. Neonatal bilirubin levels and childhood asthma in the US Collaborative Perinatal Project, 1959-1965. *Am J Epidemiol* 2013; 178: 1691-7.
8. Pietrangelo A. Hereditary hemochromatosis-a new look at an old disease. *N Eng J Med* 2004; 350: 2383-97.