CEOG Clinical and Experimental Obstetrics & Gynecology

Case Report

The course and outcome of pregnancy in patient with concomitant Gilbert syndrome and hereditary spherocytosis: a unique case report

G. Bapayeva[1], M. Terzic[1,2,3], K. Togyzbayeva[1], A. Bekenova[2], S. Terzic[2]

[1]National Research Center of Mother and Child Health, University Medical Center, Astana
[2]Department of Medicine, Nazarbayev University, School of Medicine, Astana (Kazakhstan)
[3]Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburg School of Medicine, Pittsburg, Pennsylvania (USA)

Summary

Gilbert syndrome (GS) is an autosomal dominant mild unconjugated hyperbilirubinemia. Hereditary spherocytosis (HS) is an inherited condition of non-immune heterogeneous hemolytic anemia. These two diseases can be very rarely diagnosed in one patient, but there is not one case reported in pregnant patient. The authors present a unique case of concomitant both diseases in pregnancy. The patient was 25- years-old, conceived spontaneously, and carefully observed throughout the pregnancy. Considering that both diseases might have a detrimental influence on pregnancy course and outcome, especially in this case with severe form of HS, the woman was hospitalized and carefully observed until the end of pregnancy. She delivered vaginally without any feto-maternal complications. In conclusion, co-existing GS and HS during pregnancy deserve careful monitoring and up-to-date treatment. This case report shows that a contemporary approach to the pregnant patient with GS and HS can result in the delivery of a healthy baby without any complications.

Key words: Gilbert syndrome; Hereditary spherocytosis; Pregnancy outcome; High-risk pregnancy.

Introduction

Gilbert syndrome (GS) is one of the genetic diseases affecting bilirubin metabolism. Its mode of inheritance is autosomal dominant [1]. This condition is characterized by mild unconjugated non-hemolytic hyperbilirubinemia with no deteriorating effect on liver, such as hepatic inflammation, liver failure or any chronic liver disease [2]. Hereditary spherocytosis (HS) is an inherited condition of non-immune heterogeneous hemolytic anemia [3]. Symptoms can vary from patient to patient depending on the severity of the disease and include anemia, jaundice, and splenomegaly [4].

Coexistence of these two diseases is a very rare condition, and some of the cases were reported in pediatric, adolescent, and adult non-pregnant patients [5-9]. However, according to the current literature review, the case of GS with concomitant HS has not been reported in pregnancy. The aim of this report was to present the course and outcome of pregnancy in patient with concomitant HS and GS.

Case Report

A 25-year-old G2P0 patient was referred to this clinic due to coexistent GS and HS at 37w6d of gestation. She had complaints of leg edema. Moreover, the patient had allergies to a number of medications including penicillins, cephalosporins, NSAIDs, azithromycin, tetrazine-containing medications, and atracurium bezilate with the reaction in form of urticaria and anaphylactic shock. The diagnosis of GS was made in 2009 clinically and confirmed by molecular-genetic test in September 2017: mutation 2g37 (UGT1A1) – UGT1A1 (TA) 6/ (TA)7, which is consistent with heterozygous mutation. The diagnosis of HS was done in 2013, at age 21, based on laboratory values and clinical symptoms at that time. For the second condition - HS, the patient underwent synchronous splenectomy and cholecystectomy in 2013.

The patient's first pregnancy was terminated in 2016 at gestational age of 12 weeks due to her co-existing diseases. At the time of second pregnancy, according to law in Kazakhstan, her conditions were regarded as a relative contraindication for pregnancy, so the patient decided to continue this pregnancy under careful supervision of doctors. On physical examination she was conscious, with mild skin jaundice and icteric sclera, T 36.4C, HR 77 bpm, and BP 110/70 mmHg. Uterus size corresponded to amenorrhoea. Laboratory values were significant for severely low Hb concentration (7.5 g/dL), increased MCV (126 fL), low erythrocyte levels (1.82*1012/L), and leukocytosis (20.65*109/L), and reticulocytosis ($0.31*10^9$/L). Biochemical analysis revealed elevated total bilirubin level (47.6 mcmol/L) and direct bilirubin (15.10 mcmol/L), high lactate dehydrogenase level (314 U/L), low haptoglobin (0.01 g/L). Fetal Ultrasound showed a single live fetus corresponding to dates with adequate amount of amniotic fluid and nuchal cord. Due to her diseases and gestational hypertension, the patient was treated with folic acid, aspirin, methyldopa, and amlodipine.

At 40th week of gestation patient began to have regular uterine contractions and vaginally delivered a healthy female baby with

Revised manuscript accepted for publication January 23, 2018

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVI, n. 2, 2019
doi: 10.12891/ceog4599.2019

7847050 Canada Inc.
www.irog.net

Published: 10 April 2019

Apgar score 8/9, weight 2975 grams, and length of 52 cm. Both mother and baby were fine after delivery. In the neonatal unit the baby was observed for signs of hyperbilirubinemia for four days. As laboratory results of baby were within normal range, the patient was discharged with her child on day 4 after delivery. She was advised for a regular check-up at her Ob/Gyn clinician, gastroenterologist/hepatologist, and hematologist, and to take iron and folic acid supplementation.

Discussion

GS is a benign condition of mild unconjugated hyperbilirubinemia with no deteriorating effect on liver. Approximately 7% of a general population has this disease, with men being more commonly affected than women (ratio 2-7:1) [10].

GS has an autosomal dominant mode of inheritance, and patients can be either homozygous or heterozygous (two different alleles in one locus) [11]. There are more than 100 different mutations linked to GS and their frequencies very among different populations [12]. The most common genotype among Caucasians with GS is the homozygous polymorphism of two extra bases (TA) in the TATAA box sequence of the promoter region of the UGT1A1 gene, resulting in a sequence of A(TA)7TAA (also known as UGT1A1*28) instead of the normal A(TA)6TAA [13,14,15]. In the Asian population, however, the incidence is much lower, and polymorphisms vary [16]. In our patient UGT1A1 (TA)6/ (TA)7 genotype was identified and the diagnosis was established in 2017. In this situation, the function of UGT-A1 was mildly reduced.

HS is characterized by non-immune hemolytic anemia with a prevalence of 1:2000-5000 in the Caucasian population. The exact data is not available for Asian population. The true value can be even higher due to under-diagnosis of mild forms of the disease. HS has a very broad spectrum of clinical severity due to a different extent of the mutation; disease course can range from completely asymptomatic to severe transfusion-requiring anemia [17]. Different clinical courses can be observed even within one family, which can be explained by co-inheritance of genetic variants involved in defect of erythrocytes or in other diseases, such as thalassemias or GS [6].

Diagnosis of HS is complex and can be made based on pericheral blood examination, hematological indices, reticulocyte count, the auto-hemolysis test, and others. It is important to exclude other hemolytic conditions, such as autoimmune hemolytic anemia or hemoglobinopathies. These test are not very sensitive or specific, so mild and moderate courses of HS can be missed [18]. HS can be confirmed by sodium dodecyl sulfate polyacrylamide gel electrophoresis analysis of erythrocytes membrane proteins. This test can identify a specific protein deficiency responsible for the disease; however, this test is not available everywhere [3]. In the present patient, diagnosis of HS was established at 21 age based on her clinical symptoms.

Several up-to-date articles suggest that splenectomy is a very effective surgical treatment of moderate and severe forms of HS [19, 20]. Explanation for therapeutic result of this procedure is based on the evidence that abnormal or damaged red blood cells passing through the spleen red pulp are removed by the splenic macrophage system. However, there are concerns regarding short- and long-term risks and benefits of surgery [21]. Following these up-to-date recommendations that also existed few decades ago, in the present patient, splenectomy was performed in 2013.

Gilbert genotype was significantly associated with the cholelithiasis risk in otherwise phenotypically normal adults [1]. The present patient also had gallbladder stones.

Synchronous splenectomy in patients with mild HS and symptoms of gallstone disease was performed according to the recommendations and expert guidelines existing in the adolescent period of the patient. Following these guidelines the patient underwent synchronous splenectomy and cholecystectomy. In order to check if the procedure of synchronous splenectomy during cholecystectomy for HS is really necessary, one large retrospective study was performed and found that the need for splenectomy in patients with mild HS and symptomatic cholelithiasis should be assessed on a case by case basis. The recommendation of this report is to not perform synchronous splenectomy in conjunction with cholecystectomy for these patients if no indication for splenectomy exists [22].

The influence of GS on pregnancy is usually minimal due to mild hyperbilirubinemia associated with the disease. Symptoms can aggravate in case of stress, infection or dehydration, so pregnancy, being a condition of physiologic immunodeficiency and stress, can indirectly provoke symptoms of hyperbilirubinemia.

Considering HS, according to current criteria [23], the present patient had a severe form of the disease, which can have a severe deteriorating influence on fetal conditions, especially due to severe hemolytic anemia.

Conclusion

In conclusion, this case represents a unique case of co-existing GS and HS during the pregnancy. Both diseases deserve careful monitoring and up-to-date approach, especially during pregnancy. This case report shows that contemporary approach to the pregnant patient with GS and HS can result in the delivery of a healthy baby without any complications.

References

[1] Fretzayas A., Moustaki M., Liapi O., Karpathios T. "Gilbert syndrome". *Eur. J. Pediatr.,* 2012, *171*, 11.

[2] Strassburg C.P.: "Pharmacogenetics of Gilbert's syndrome". *Pharmacogenomics*, 2008, *9*, 703.

[3] Farias M.G.: "Advances in laboratory diagnosis of hereditary sphe-

rocytosis". *Clin. Chem. Lab. Med.,* 2017, *55*, 944.
[4] Bolton-Maggs P.H., Langer J.C., Iolascon A., Tittensor P., King M.J.: "General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis and management of hereditary spherocytosis - 2011 update". *Br. J. Haematol.,* 2012, *156*, 37.
[5] Aiso M., Yagi M., Tanaka A., Miura K., Miura R., Arizumi T., *et al.*: "Gilbert Syndrome with Concomitant Hereditary Spherocytosis Presenting with Moderate Unconjugated Hyperbilirubinemia". *Intern. Med*., 2017, *56*, 661.
[6] Jamwal M., Aggarwal A., Kumar V., Sharma P., Sachdeva M.U., Bansal D., *et al.*: "Disease-modifying influences of coexistent G6PD-deficiency, Gilbert syndrome and deletional alpha thalassemia in hereditary spherocytosis: A report of three cases". *Clin. Chim. Acta.,* 2016, *458*, 51.
[7] Lee J.H., Moon K.R.: "Coexistence of gilbert syndrome and hereditary spherocytosisin a child presenting with extreme jaundice". *Pediatr. Gastroenterol. Hepatol. Nutr.,* 2014, *17*, 266.
[8] Lee M.J., Chang Y.H., Kang S.H., Mun S.K., Kim H., Han C.J., Kim J., Kang H.J.: "A Case of hereditary spherocytosis coexisting with Gilbert's syndrome". *Korean. J. Gastroenterol.* 2013, *61*, 166.
[9] Garg P.K., Kumar A., Teckchandani N., Hadke N.S.: "Hereditary spherocytosis coexisting with Gilbert's syndrome: a diagnostic dilemma". *Singapore. Med. J.,* 2008, *49*, 308.
[10] Mohan M., P L.S., Reddy P.V.: "Pregnancy with gilbert syndrome - a case report". *J. Clin. Diagn. Res.,* 2014, *8*, 1.
[11] Bosma P.J.: "Inherited disorders of bilirubin metabolism". *J. Hepatol*., 2003, *38*, 107.
[12] Strassburg C.P.: "Hyperbilirubinemia syndromes (Gilbert-Meulengracht, Crigler-Najjar, DubinJohnson, and Rotor syndrome)". *Best Pract. Res. Clin. Gastroenterol.,* 2010, *24*, 555.
[13] Bosma P.J., Chowdhury J.R., Bakker C., Gantla S., de Boer A., Oostra B.A., *et al.*: "The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome". *N. Engl. J. Med.,* 1995, *333*, 1171.
[14] Beutler E., Gelbart T., Demina A.: "Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism?" *Proc. Natl. Acad. Sci. U S A*, 1998, *95*, 8170.
[15] Memon N., Weinberger B.I., Hegyi T., Aleksunes L.M.: "Inherited disorders of bilirubin clearance". *Pediatr. Res.,* 2016, *79*, 378.
[16] Wang X., Liu Y., Chang Y., Liu H., Wang P.: "Diagnosis and treatment of a 16-year-old Chinese patient with concurrent hereditary hemochromatosis and Gilbert's syndrome". *Eur. J. Med. Res.*, 2014, *19*, 51.
[17] Narla J., Mohandas N.: "Red cell membrane disorders". *Int. J. Lab. Hematol.,* 2017, *39*, 47.
[18] Crisp R.L., Solari L., Vota D., García E., Miguez G., Chamorro M.E., *et al.*: "A prospective study to assess the predictive value for hereditary spherocytosis using five laboratory tests (cryohemolysis test, eosin-5′-maleimide flow cytometry, osmotic fragility test, autohemolysis test, and SDS-PAGE) on 50 hereditary spherocytosis families in Argentina". *Ann. Hematol.,* 2011, *90*, 625.
[19] Manciu S., Matei E., Trandafir B.: "Hereditary Spherocytosis - Diagnosis, Surgical Treatment and Outcomes. A Literature Review". *Chirurgia (Bucur)*, 2017, *112*, 110
[20] Iolascon A., Andolfo I., Barcellini W., Corcione F., Garçon L., De Franceschi L., *et al.*: "Recommendations regarding splenectomy in hereditary hemolytic anemias". *Haematologica*, 2017, *102*, 1304.
[21] Rice H.E.: "Understanding splenectomy for children with hereditary spherocytosis". *Pediatr. Blood. Cancer.,* 2016, 63, 1700.
[22] Ruparel R.K., Bogert J.N., Moir C.R., Ishitani M.B., Khan S.P., Rodriguez V., Zarroug A.E.: "Synchronous splenectomy during cholecystectomy for hereditary spherocytosis: is it really necessary?" *J. Pediatr. Surg.,* 2014, *49*, 433.
[23] Verma P., Kulkarni S.R.: "Pregnancy complicated with hereditary spherocytosis – lessons learnt from a case and review of literature". *Int. J. Adv. Res.,* 2016, *4*, 1245.

Corresponding Author:
M. TERZIC, M.D., PHD, OB/GYN
Nazarbayev University School of Medicine
5/1 Kerey and Zhanibek Khans Street
NUSOM Building Office 904/9
Astana, 010000 (Kazakhstan)
e-mail: terzicmilan@yahoo.co.uk