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Hereditary Spherocytosis with Gilbert's Syndrome – a case report.

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Abstract:
A 23 year old previously diagnosed female with Gilbert's syndrome on treatment with Prednisone, presented with a lower respiratory tract infection for the past 4 days with additional complaints of significant lethargy and fatigue, palpitation and intermittent yellowish discolouration of sclera since 9 years old. The patient's mother and elder sister also had similar history of intermittent jaundice. Routine investigations of the patient revealed normal values except a hemoglobin level of 6.0 g/dl, HCT of 19.5%, MCV of 75.6 fL, serum total bilirubin of 6.3 mg/dl (Direct: 1.3mgdl, Indirect: 5.0 mg/dl). This made us suspect another basic hematologic abnormality that contributed to such elevated indirect bilirubin levels. Further investigations revealed a peripheral smear with moderate microcytic hypochromic anemia, anisopoikilocytosis, leucopenia and a reticulocyte count of 2.3%, negative Direct coombs test and a serum LDH of 345U/L. Ultrasound sound abdomen revealed multiple calculi in gall bladder largest measuring 3mm and splenomegaly. Peripheral smear was repeated only to reveal a dimorphic blood picture with eosinophilia, normocytic normochromic anemia with a few fragmented RBCs and spherocytes. The patient was suggested hemoglobin electrophoresis and Osmotic fragility test. Osmotic fragility was found to be increased suggested from the hemolysis which started at 0.6% hypotonic saline and completed at 0.4%. A final diagnosis of non-immune hemolytic anemia due to hereditary spherocytosis co-existing with Gilbert syndrome was established. Splenectomy was suggested due to severe anemia and hemolysis. Before the new diagnosis, the patient wasn't aware that her refractory anemia could be treated with Splenectomy that could possibly clear the symptoms with appropriate post splenectomy vaccination and monitoring, thus explaining how diagnostic difficulties with such underlying conditions could affect the patient's wellbeing.

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I. Introduction:

Intermittent unconjugated hyperbilirubinemia in the absence of a liver disease or hemolysis presenting in childhood is characteristic of Gilbert syndrome(GS). It is the most common inherited metabolic liver disorder occurring in 5-6% of the population, caused by a genetic mutation of the gene UDP-glucuronosyl transferase UGT1A1[1] resulting in decreased activity of the enzyme that conjugates the bilirubin and an impairment of this enzyme leads to mild hyperbilirubinemia usually less than 6mg/dl. Hereditary spherocytosis(HS) is an abnormality of the erythrocyte membrane protein resulting in the loss of membrane and changing of shape[2]. These abnormally shaped erythrocytes or spherocytes undergo hemolysis in the spleen leading to elevated unconjugated hyperbilirubinemia. Gilbert syndrome and hereditary spherocytosis are usually common among the population. Coexisting of these conditions is not so common but there has been a recent trend in such occurrence and it makes us rethink the original diagnosis in both conditions.[3]

II. Case Report

A 23 year old female came to the outpatient clinic with complaints of fever and cough with expectoration for the past 4 days and yellowish discolouration of the sclera, intermittent since nine years old. Past history revealed that she was diagnosed with Gilbert syndrome few years back after an episode of jaundice. Her mother and elder sister also had similar symptoms of intermittent jaundice in the past. It was thought that her present jaundice was due to a mild bronchitis triggering hyperbilirubinemia as it would occur in Gilbert

syndrome. Upon general examination, she was icteric and pallor was present. Abdomen examination revealed mild splenomegaly. Routine investigations were done and the findings are listed below.

Complete blood count:

Hemoglobin	6.0 g/dl
RBC	2.58 million/cu.mm
WBC	3800 cells/cu.mm
HCT	19.5%
MCV	75.6fL
MCHC	34.4 g/dl
Platelet count	2,18,000/cu.mm

Renal function test

Random blood sugar	107mg/dl
Urea	29mg/dl
Creatinine	0.7mg/dl
Sodium	138meq/l
Potassium	3.9 meq/l

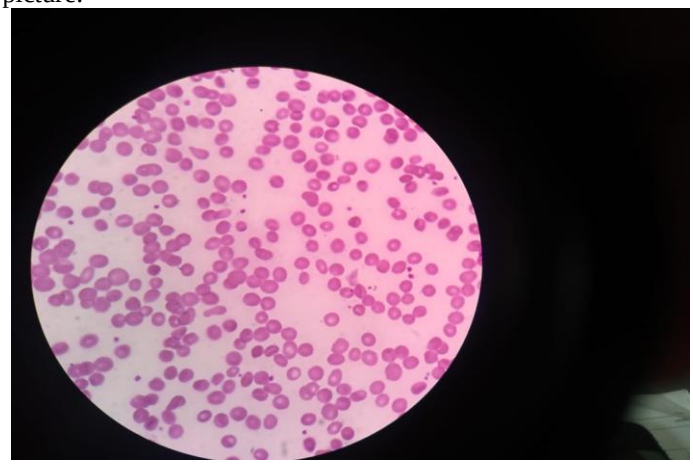
Liver function test

Serum bilirubin Direct Indirect	6.3mg/dl 1.3mg/dl 5.0mg/dl
SGOT	52U/L
SGPT	17U/L
Serum ALP	44U/L
Total protein	7.4g/dl
Albumin	4.4g/dl
Globulin	3.0g/dl

Other investigations

Peripheral blood smear	Dimorphic blood picture with mild eosinophilia, few microspherocytes, and fragmented erythrocytes.(refer image below)
Reticulocyte count	2.4%
Direct Coombs test	Negative
Serum LDH	345U/l
USG Abdomen	Multiple calculi in the gall bladder largest measuring 3mm, mild splenomegaly

Peripheral blood smear picture:



After obtaining hematologist opinion, Hemoglobin electrophoresis was done [HbA – 93.8 (96.8 – 97.8) HbA2 – 1.3 (2.2 – 3.2)]. Osmotic fragility test was done which started at 0.6% hypotonic saline and ended at 0.4%. This increased osmotic fragility with other features in this patient with anemia, gall stones, splenomegaly, indirect hyperbilirubinemia, direct coombs test, elevated serum LDH levels, elevated

reticulocyte count with microspherocytes in peripheral smear and a negative direct coombs test with a positive family history suggest that this patient had a Non Immune hemolytic anemia due to Hereditary Spherocytosis coexisting with Gilbert syndrome[4].

III. Discussion:

Previously, GS combined with HS was considered to be rare, because only single cases had been reported. Indeed, from the individual prevalence rates (GS, approximately 2% to 20%; HS, 1 per 2000 persons), the calculated rate of coexistence of GS and HS is low (10 to 100 per million births). However, new cases are being studied widely all over the world, strongly indicating that this phenomenon might not be uncommon in a specific subset of population like isolated hyperbilirubinemia, which mainly includes GS and chronic hemolysis. Perhaps a number of cases were missed because of a lack of awareness and available techniques.

GS is characterized by mild to moderate, chronic unconjugated hyperbilirubinemia in the absence of overt hemolysis or structural liver disease[5]. The reported prevalence is as high as approximately 2% to 20%[1]. Patients with GS typically present when isolated hyperbilirubinemia is detected as an incidental finding on routine multiphasic biochemical screening, and clinical jaundice is uncommon. Except for the finding of icterus or jaundice, patients are usually asymptomatic. Jaundice often worsens in response to fasting, stress, dehydration, menstruation, or overexertion[6]. Family history is often positive. Low calorie intake test and phenobarbital stimulation test were the common diagnostic tests used in the past, and they have been gradually replaced by simple and reliable detection of *UGT1A1* gene mutation[7,8]. Although GS has generally been thought to be an entirely benign condition with no necessary treatment, persons with this disorder may be at increased risk for gallstones and for the toxicity of selected drugs like irinotecan that require glucuronidation for metabolic disposal[9].

HS is a common congenital hemolytic disease involving intrinsic abnormalities of RBC membrane proteins that alter RBC morphology, resulting in spheroid, rather than disc-shaped RBCs, which are thus less deformable than normal RBCs and more vulnerable to splenic sequestration and destruction. Typically, patients with HS have icterus, anemia, and splenomegaly due to chronic hemolysis. Most patients diagnosed with HS have a positive family history. The most common complication of HS is the formation of bilirubinate gallstones, which occurs in about half of HS-diagnosed patients[10]. A substantial number of spherocytes in peripheral blood smears is a key diagnostic indicator of HS. Splenectomy can be performed to alleviate anemia and prevent gallstone formation. Genetic mutations that affect RBC membrane proteins [*e.g.*, ANKs, spectrins, band 3, and/or (rarely) protein 4.2] cause HS. The clinical presentation and severity of HS symptoms are highly variable across patients depending upon which of these mutations, and how many of them, are present. HS diagnoses may be missed in mild cases due to there being few spherocytes in peripheral blood smears. Furthermore, in patients with well-compensated hemolysis, signs of HS may only be detected when complications occur. Currently, a definitive diagnosis of HS requires RBC membrane protein electrophoresis or genetic testing[11].

GS has been suspected in some patients already diagnosed with HS because of high serum bilirubin levels in the absence of pronounced anemia[4]. In other cases, poor responses to hemolytic therapies, such as persistent hyperbilirubinemia after splenectomy or ineffective phototherapy for neonatal jaundice, have provided important diagnostic clues. Some patients with GS are examined for comorbidity of hemolytic disease (including HS) based on an elevated reticulocyte ratio, low hemoglobin, or splenomegaly[4]. However, a few perceptive doctors suspected the coexistence of GS and HS when they encountered an isolated hyperbilirubinemia with hemolytic signs by carefully evaluating inappropriately elevated bilirubin level compared with the degree of hemoglobin.

An abnormally short RBC lifespan is a defining characteristic of hemolysis. However, standard RBC lifespan measurement techniques (*e.g.*, isotope or biotin labeling quantitation) are not amenable to routine clinical practice because they are cumbersome and time-consuming[12]. Based on hemoglobin degradation dynamics, Levitt and colleagues[13] developed a simple and accurate CO breath test method for determining RBC lifespan, which was subsequently adapted to an automated instrument that can report RBC lifespan within 15 min. Investigations of this kind can help the clinicians identify such coexisting hemolysis in patients with Gilbert's syndrome.[3]

References:

[1]. Bosma PJ, Chowdhury JR, Bakker C, Gantla S, de Boer A, Oostra BA, Lindhout D, Tytgat GN, Jansen PL, Oude Elferink RP. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N Engl J Med*. 1995;333:1171-1175.

[2]. Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis. *Lancet*. 2008;**372**:1411-1426.

[3]. Kang LL, Liu ZL, Zhang HD. Gilbert's syndrome coexisting with hereditary spherocytosis might not be rare: Six case reports. *World J Clin Cases* 2020; 8(10): 2001-2008.

[4]. Garg PK, Kumar A, Teckchandani N, Hadke NS. Hereditary spherocytosis coexisting with Gilbert's syndrome: a diagnostic dilemma. *Singapore Med J*. 2008;49:e308-e309

[5]. Strassburg CP. Hyperbilirubinemia syndromes (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor syndrome). *Best Pract Res Clin Gastroenterol*. 2010;24:555-571.
[6]. Rodrigues C, Costa E, Vieira E, Santos R, De Carvalho J, Rocha-Pereira P, Santos-Silva A, Bronze-da-Rocha E. Bilirubin dependence on UGT1A1 polymorphisms, hemoglobin, fasting time and body mass index. *Am J Med Sci*. 2012;343:114-118.
[7]. Torres AK, Escartín N, Monzó C, Guzmán C, Ferrer I, González-Muñoz C, Peña P, Monzó V, Marcaida G, Rodríguez-López R. Genetic susceptibility to Gilbert's syndrome in a valencian population; efficacy of the fasting test. *Rev Clin Esp*. 2017;217:1-6.
[8]. Minucci A, Concolino P, Giardina B, Zuppi C, Capoluongo E. Rapid UGT1A1 (TA)(n) genotyping by high resolution melting curve analysis for Gilbert's syndrome diagnosis. *Clin Chim Acta*. 2010;411:246-249.
[9]. Mehra R, Murren J, Chung G, Smith B, Psyrri A. Severe irinotecan-induced toxicities in a patient with uridine diphosphate glucuronosyltransferase 1A1 polymorphism.
[10]. Trompeter S, King M. Hereditary spherocytosis. *Paediatr Child H (United Kingdom)*. 2019;29:359-364.
[11]. Bolton-Maggs PH, Stevens RF, Dodd NJ, Lamont G, Tittensor P, King MJ; General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis and management of hereditary spherocytosis. *Br J Haematol*. 2004;126:455-474
[12]. Cartei G, Chisesi T, Cazzavillan M, Barbui T, Battista R, Vianello Dri A, Dini E. Red blood cell survival and hyperbilirubinaemia in the Gilbert's syndrome. *Folia Haematol Int Mag Klin Morphol Blutforsch*. 1976;103:93-100.
[13]. Strocchi A, Schwartz S, Ellefson M, Engel RR, Medina A, Levitt MD. A simple carbon monoxide breath test to estimate erythrocyte turnover. *J Lab Clin Med*. 1992;120:392-399.

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