



## RESEARCH ARTICLE

### HEREDITARY SPHEROCYTOSIS AND GALLSTONES FORMATION

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#### ABSTRACT

Hereditary spherocytosis (HS) is a heterogeneous group of hemolytic anemia caused by deficiency or dysfunction of red blood cell (RBC) cytoskeletal proteins. It is a common disorder located mostly in Caucasian population; most affected individuals have mild or only moderate hemolysis. In a few rare cases, the measurement of RBC membrane proteins is required to clarify the nature of the membrane disorder in absence of the family history. Patients with HS are at more risk of developing gallstones, whose prevention represents a major impetus for splenectomy in such patients. The main purpose of the study is to perform a mini review on the formation of gallstones in patients with hereditary spherocytosis. Hence, regular ultrasound and other diagnostic examinations are recommended for timely detection of any presence of gallstones in patients with HS.

#### INTRODUCTION

Primary red blood cell (RBC) membrane disorders lead to numerous clinical syndromes including hereditary spherocytosis (HS) (Da Costa *et al.*, 2013). HS syndromes are considered as a group of inherited disorders associated with a primary defect in RBC membrane proteins (Parrotta *et al.*, 2008). They are characterized by the presence of sphere-shaped erythrocytes on the peripheral blood (PB) smear (Eber and Lux, 2004). Globally, this disorder is found in all kinds of racial and ethnic groups, and is one of the most commonly inherited anemia that affects approximately 1:1000-2500 individuals of the Northern European descent (Gallagher, 2005).

#### Pathophysiology

The main cellular defect in hereditary spherocytosis includes the loss of membrane surface area related to intracellular volume, which results in spherical shaped RBCs with decreased deformability of the RBC (Gallagher, 2004). The increase in membrane fragility led by the defects in erythrocyte membrane proteins result in the loss of their surface area (Mohandas and Gallagher, 2008). The increased fragility further leads to vesiculation and loss of erythrocyte membranes, which is the main cause of hemolysis (Lusher and Barnhart, 1980; Safeukui *et al.*, 2012).

Defects of the membrane proteins, including band 3 protein,  $\alpha$  spectrin,  $\beta$  spectrin, protein 4.2, or ankyrin results in erythrocyte membrane loss (Parrotta *et al.*, 2008; Gallagher, 2004). RBC membranes of the HS patients show quantitative and qualitative abnormalities of the aforementioned proteins. The most common abnormality is the combined deficiency of spectrin and ankyrin, followed by band 3 protein, isolated spectin, and protein 4.2 (Gallagher, 2005). Therefore, the genes responsible for HS include  $\alpha$  spectrin,  $\beta$  spectrin, ankyrin, band 3 protein, and protein 4.2 (Gallagher, 2004). Studies have also concluded that two thirds of typical HS patients have inherited the mutated genes in an autosomal dominant manner (Parrotta *et al.*, 2008). Ankyrin mutations in this group of patients are the most frequent cause of the HS disease, followed by mutations in  $\beta$  spectrin and band 3 protein. On the other hand, inheritance in the remaining group of patients is non-dominant due to de novo mutation or autosomal recessive inheritance. The autosomal recessive inheritance is caused either due to the mutations of either the protein 4.2 or  $\alpha$  spectrin genes (Eber and Lux, 2004; Gallagher, 2004; Giudice *et al.*, 1998a,b).

#### Clinical Manifestations

Clinical manifestations of HS vary widely and may occur at any age; however it occurs typically during childhood stages. HS is basically associated with hemolysis, anemia, pallor, jaundice, splenomegaly, and reticulocytosis. The presence of spherocytosis is evident from the peripheral blood film along with increased osmotic fragility and positive family history of HS (Eber *et al.*, 1990).

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The degree of hemolysis varies widely ranging from incidentally diagnosed asymptomatic HS patients to severe, transfusion-dependent HS patients (Gallagher, 2013).

### Complications of HS

The HS complications include cholelithiasis, cholecystitis, biliary obstruction and cholangitis (Tamary *et al.*, 2003). Furthermore, these patients may suffer from aplastic, hemolytic, and megaloblastic crises. Aplastic crisis, occurred after virally-induced bone marrow (BM) suppression mainly by human parvovirus B19, may lead to serious complications of severe anemia including congestive heart failure or even death. On the other hand, the long-term disorder hemolytic crisis is characterized by the increased splenomegaly, anemia, jaundice, and reticulocytosis. Patients with increased folate demand, e.g., growing children, pregnant women, or elderly people develop megaloblastic anemia (Gallagher, 2005).

### INITIAL ASSESSMENT & LABORATORY FINDINGS IN HS

The initial assessment of patients with suspected HS includes the medical history of their family members about the occurrences of anemia, gallstones, jaundice, and splenomegaly. Physical examinations also draw attention to the signs of any disorder like jaundice, splenomegaly, and scleral icterus.

Patients with typical HS contain obvious spherocytes that lack central pallor on the PB smear, and most of the HS patients suffer from mild to moderate anemia with reticulocytosis (Rocha *et al.*, 2005; Guarnone *et al.*, 1996). In approximately 50% of HS patients, the mean corpuscular hemoglobin concentration (MCHC) increases due to relative cellular dehydration (Michaels *et al.*, 1997). The red cell distribution width (RDW) also increases (>14) in these patients (Michaels *et al.*, 1997; Cynober *et al.*, 1996). The incubated osmotic fragility (OF) test is the gold standard test for diagnosing HS in patients with Coombs-negative spherocytic hemolytic anemia (HA). After incubating HS erythrocytes at 37°C for 24 hours, they start losing their membrane surface area more readily than that of normal cells because of their unstable and leaky characteristics (Gallagher, 2005). However, the results of this OF test suffer from poor sensitivity as nearly 20% of the mild HS cases are missed out after this incubation period. Recently, eosin-5-maleimide test has been explored as a screening test for HS diagnosis by conducting the flow cytometric analysis of the dye that binds with the erythrocytes (King *et al.*, 2004). The increased level of bilirubin, reticulocytosis, lactate dehydrogenase (LDH), fecal, and urinary urobilinogen along with the decreased level of haptoglobin reflects the increased erythrocyte production or destruction in HS patients (Gallagher, 2005).

### DISCUSSION

The development of bilirubin gallstones is considered as one of the most common complications of HS (Gallagher and Forget, 1998). About 6-50% of HS patients develop symptomatic gallbladder disease and experience cholecystectomy at the age of 10-30 years old (Bates and Brown, 1952; Alizia *et al.*, 2010). On the other hand, only 5-8% of children below 10 years of age have noticeable gallstones (Pinto *et al.*, 1995).

Therefore, the mean age for diagnosis of cholelithiasis is inversely proportional to the severity of the disease (Tamary *et al.*, 2003). Pigmented gallstones develop in children between the age group of 4-5 years old and eventually around 50% of the unsplenectomized patients form gallstones even though the patients are asymptomatic. The frequency of gallstones is not common in children below the age group of 10 years old; however, is present in at least half of the adults with severe haemolytic anemia (Kar *et al.*, 2009). The gallstones leads to the development of jaundice, thereby, improving the haemolytic process and normalizes OF (Cooper and Jandl, 1969). Furthermore, the abnormal plasma lipid profile increases the membrane surface area that normalizes the formerly reduced surface area-to-volume ratio owing to loss of the membrane surface area in the spherocytes. The occurrence of gallstones is increased more if the patient with HS co-inherits the genetic defect resulting in the reduced activity of the bilirubin conjugating enzyme uridine diphosphate-glucuronyltransferase, i.e., Gilbert syndrome (Abdullah *et al.*, 2015). del Giudice *et al.* (1999) reported that in a study of 102 children from southern Italy with mild to moderate HS, gallstones were found in 12% normal patients, 26% heterozygous patients, and 48% homozygous patients for the Gilbert syndrome mutation. But, no significant dissimilarity in the degree of hemolysis or the age of onset of gallstones as measured by average reticulocyte count. The most excellent method to detect gallstones is ultrasonography. An abdominal ultrasound is optional in every third to fifth year of HS detection and before splenectomy. Eventually, around 40-50% of patients with gallstones develop symptoms of gallbladder disorder or biliary obstruction. The treatment of gallbladder disorder is controversial, particularly in patients with asymptomatic or mild HS gallstones (Eber & Lux, 2004). Cholecystectomy is suggested for patients with symptomatic gallstones with recurrent biliary colic or cholecystitis. Combined surgical procedures of cholecystectomy and prophylactic offer a considerable gain in the life expectancies of young patients and adults having mild HS and gallstones (Marchetti *et al.*, 1998; Al-Salem *et al.* 1997.). Yet, the use of concomitant splenectomy is controversial and considered on an individual basis, considering the severity of HA versus the post-splenectomy risks (Kruger and Burgert, 1966; Alizia *et al.*, 2010; Kar *et al.*, 2009; Oliveria *et al.*, 2012).

### Conclusion

The red blood cell membrane diseases like hereditary spherocytosis are inherited because of the mutations in various membrane proteins, thereby, resulting in the decreased red cell deformability, reduction in the life span, and premature removal of the red cells from the circulation. The variations in the incidences of gallstones or cholelithiasis are in accordance with the different types of inherited hemolytic disorders and the ethnicity of the patients with HS. Therefore, regular ultrasound and other diagnostic examinations are recommended for timely detection of any presence of gallstones in patients with HS.

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