GALLSTONES IN PATIENTS WITH INHERITED HEMOLYTIC DISEASES

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ABSTRACT

The purpose is to provide an overview on the incidence of gallstone disease in patients with various types of inherited (chronic) hemolytic diseases at risk of cholelithiasis/choledocholithiasis with particular emphasis on its pathogenesis, genetic, risk factors and management. A detailed electronic literature search to determine the source of materials for this review article was done. The reported incidences of gallstones and choledocholitisis vary according to the different types of inherited hemolytic diseases and the ethnicity of the studied populations. The reported incidences of gallstones in different types of inherited hemolytic diseases are: 4-85 % in Sickle Cell Anaemia (Hb-SS), 29 % in Sickle Cell Trait (Hb-AS), 23 % in Sickle Cell Hemoglobin-C (Hb-SC), 12 % in Hb S-B-Thalassaemia, 4-61 % in Hereditary Spherocytosis, 30->80 % in beta thalassaemia Major, 23-57 % in beta-thalassaemia Intermedia, 21 % in beta-thalassaemia Minor (Trait). Chronic hemolysis leads to increased bilirubin excretion and pigment gallstones formation, thus patients who are homozygous have the higher incidence of gallstones development than those who are heterozygous for that particular gene defect and disease, and there is a general trend in this direction. The incidence of gallstones increased in the last years [1]. To date, no review article summaries the incidences of cholelithiasis in patients with various inherited haemolytic diseases. A detailed electronic literature search to determine the source of materials for this report was done. Keywords used for websites searching were "Gallstones, cholelithiasis, choledocholithiasis, haemolytic diseases." The Pro Quest Hospital Collection and NCBI search were the principal sources of information. All searches limited to research published in English. In addition, the Google Scholar search engine used in the search. The resulting literature involved over 700 peer-reviewed journal articles. Out of the total 100 reviewed and analyzed articles, 62 selected articles were included in this report. In addition, review articles were included in the references because they provided contextual material for the review.

Aetiology and pathogenesis

The pathogenesis of biliary calculi in the various inherited chronic haemolytic anaemias is not understood clearly. In haemolytic anemias, the liberated hemoglobin is broken down, and its heme component is eventually, degraded into bilirubin by the liver. The development of pigmented gallstones due to chronic hemolysis is age-dependent. Etiologically, cholelithiasis is divided into three groups; haemolytic, other known etiology, and idiopathic. A 30% of all gallstones in children are due to haemolytic diseases such as sickle-cell disease, hereditary spherocytosis and thalassemia. In about 30% of cases, gallstones are due to another known etiology such as cholestasis, chronic liver disease, prolonged fasting and ileal resection. In 40% of cases, gallstones are idiopathic mainly in adults and adolescent girls [1]. Cholesterol gallstones (green, white, or yellow stones) (pure and mixed) that are made mostly of cholesterol (70-80%), plus calcium salts and bilirubin compounds (20-30%). The pigmented stones (black or brown) contain less than 20% cholesterol and are composed mainly of bilirubin and calcium salts. Mixed gallstones composed of a mixture of the two gallstone types (fig. 1).

Mixed gallstones are the commonest stones in adults, and the pigment stones are more common in children. Cholesterol supersaturation of bile together with biliary stasis predisposes to cholesterol gallstone formation. Pigmented stones formed due to supersaturation of bile with calcium bilirubinate as in hemolytic disorders. Biliary sludge composed of mucus; calcium bilirubin and cholesterol crystals commonly associated with sickle-cell disease (fig. 2). The biliary sludge may resolve spontaneously or may progress to gallstone developet. Persistent sludge gives rise to biliary complications (such as obstruction or infection). Bilirubin converted in the hepatocytes to bilirubin monoglucuronide or di glucuronide by several classes of the enzyme glucuronosyl transferase.

The poorly soluble bilirubin is frequently present in the cholesterol stones as the bilirubin precipitates in the gallbladder and forms bilirubin stones (fig. 3). Unconjugated as well as defletively conjugated bilirubin enhances the cholesterol crystallization by direct interaction with biliary lipid or indirect alteration of biliary lipid or both [2].
It has formulated by Dewey KW and Grossman H. in 1970 [3] that the incidence of cholelithiasis in hereditary spherocytosis is higher compared to beta thalassemia major and sickle cell anemia. The proposed higher rate attributed to the concentration of hemoglobin and total hemoglobin mass. In hereditary spherocytosis, an abnormality in red cell shape is secondary to changes in the cell membrane. The spherocytic cells despite their relatively small size, contain normal to increased amounts of hemoglobin. In both thalassemias major and sickle-cell anemia, the primary defect is failure to synthesize normal adult hemoglobin either by the inability to produce beta chains or by abnormal amino acid substitutions, respectively. As a result, the red blood cells in thalassemia major are hypochromic and microcytic, thereby containing less hemoglobin; whereas in sickle-cell anemia, the total cell mass may be less because of the abnormal red cell shape. Thus, for each red blood cell hemolyzed, there is a greater amount of bilirubin produced from the cell of hereditary spherocytosis [3]. This proposal is suboptimal to explain the higher reported incidences of gallstone disease in beta thalassemia major and sickle cell anemia compared to that in hereditary spherocytosis. Moreover, genetics and other risk factors are proven to contribute toward the development and incidences of gallstone disease in various inherited chronic hemolytic disease. However, the practice of using the non-invasive and sensitive detection technique (ultrasound scan) and the longer survival of patients with inherited hemolytic diseases might explain the higher incidences of gallstone disease in beta thalassemia major and sickle cell anemia compared to that in hereditary spherocytosis. According to the physiology of macrophages and their role in the cellular protein catabolism, unstable globin is polyubiquitinated and degraded via the proteasome. If ubiquitin-proteasome activity is insufficient, unstable globin forms insoluble aggregates that serve as a substrate for macro autophagy. Chaperones are involved in refolding unstable globin or in targeting unstable globin for degradation. Accumulation of unfolded proteins activates autophagy (fig. 3). The complete breakdown of proteins requires the action of proteases capable of degrading proteins to small peptide fragments, and peptidases that hydrolyze these peptides to amino acids [4]. However, does gallstone disease is pertinent to the broader framework of protein-aggregation or metabolism disorders?. This question requires to know the sequence of proteolytic events in detail particularly in hematological diseases with insoluble/unstable globins [5, 6].

Additional studies both in laboratories and in the clinics will be necessary to appraise with accuracy the role of hemoglobin degradation products (such as hemorphins) in physiology or pathology [7]. Evaluating the role of the altered solubility of the mutated proteins and hemoglobin subunit in the red blood cells could provide additional information for the mechanism of the gallstones development in patients with inherited hemolytic diseases.

Fig. 1: (A) Cholesterol, (B) pigmented (Source: www.med.umich.edu) and (C) mixed stones (Source: health-fts.blogspot.com)

Fig. 2: (A) Biliary sludge (Source: http://www.radiologytutorials.com), (B) Multiple gallstones (Source: http://www.rcstn.net/marisa.bush)

Fig. 3: Mechanism of the extravascular hemolysis and gallstones development
Genetic and risk factors

Up to one-third of gallstones may be related to genetic factors.

1- Ethnicity: it is significant risk factors mainly in the paediatric population.

2- Mutation in the uridine diphosphate-glucuronyltransferase gene (UGT1A): This gene is a nested gene complex comprising nine transcriptional units, each encoding a specific isoform of the enzyme. UGT1A1 is responsible for bilirubin glucuronidation. The 2-bp (TA) insertion within the promoter of the UGT1A1 is associated with Gilbert syndrome. The promoter polymorphisms in the UGT1A1 gene resulted in excessive bilirubin production and associated with unconjugated hyperbilirubinemia. The latter appear to be a risk factor for symptomatic gallstones in subjects with sickle cell anemia (SCA) and hereditary spherocytosis [9]. It is reported that, children with SCA and the 7/7 promoter UGT1A1 genotype had a significantly higher mean bilirubin level than those with the 6/6 or 6/7 genotypes and were more likely to have had a previous cholecystectomy [9,10]. The presence of the 7/7 UGT1A1 genotype may also adversely affect the ability of hydroxyurea to prevent gallstone formation in SCA. Carriers of the 7/7 genotype had bilirubin levels more than 3 mg/dL despite full-dose hydroxyurea therapy while those with the 6/6 genotype had normal bilirubin levels following treatment with this agent [11]. Coinheritance of Gilbert syndrome increases the risk of developing gallstones in patients with hereditary spherocytosis. UGT1A1 gene promoter polymorphism is also a major genetic risk factor modifying the frequency and age-at-onset of cholelithiasis in patients with SCA [12]. The individual susceptibility to form gallstones from TA insertion in the TATA-box of the UGT1A1 promoter should be considered during the follow-up of patients with different forms of inherited (eg, thalassemia, intraerythrocytic enzymatic deficiency) or acquired (eg, autoimmune hemolytic anemia, hemolysis from mechanical heart valve replacement) chronic hemolysis. Homozygosity of the (TA)7 allele (also known as UGT1A1*28) has been implicated in Gilbert’s syndrome and the unusually high unconjugated bilirubinemia observed in individuals with various forms of inherited chronic hemolysis: heterozygous β-thalassemia, β-thalassemia intermedia, neonatal jaundice associated with glucose-6-phosphate dehydrogenase deficiency, hereditary spherocytosis and sickle cell anemia [12].

3- Mutation in the ATP-binding cassette transporter sub-family C member 8 (ABCG8) gene significantly increases the risk of gallstones by causing the cholesterol pump to work continuously at a high rate. A single gene, however, does not explain the majority of cases, so multiple genes and environmental factors play an intricate role.

4- Multiple blood transfusions: In patients who periodically receive blood transfusions, hemolysis of the transfused cells may supplement the chronic endogenous blood destruction as a factor in the formation of gallstones [13].

5- High rates (20%) by age of four years) of recurrent biliary tract obstruction in children with the sickle cell disease reported [14].

6- Obesity: With the prevalence of childhood obesity on the rise, there is a need to be more aware of obesity-related comorbidity including gallbladder disease. No clear link between the diet and risk for cholelithiasis, though foods high in cholesterol and low in fiber may increase the risk [15].

7- Inefficient and infrequent gallbladder contractions, which allow bile to sit in the gallbladder for long periods of time, resulting in an over concentrated bile that is conducive to stone formation [16].

8- Other risk factors include liver cirrhosis and biliary tract infections, trisomy 21 in patients with sickle cell disease and extensive small bowel resection requiring total parenteral nutrition [13].

Epidemiology

A prominent feature of children with chronic haemolytic anemia is the development of premature bilirubin gallstone disease and biliary tract inflammation. Of interest is the variation with the age of incidence of cholelithiasis in the haemolytic anemias(table 1). As patients with hemolytic anemia grow older, gallstones are more likely to develop.

Table 1: Prevalence (%) of gallstones according to the type of inherited hemolytic diseases, age group and population

<table>
<thead>
<tr>
<th>Type of inherited hemolytic diseases (%)</th>
<th>Age group</th>
<th>Population</th>
<th>Gallstones (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle Cell Anaemia (Hb-SS) [4-85]</td>
<td>Children</td>
<td>Jamaican</td>
<td>30/226 (13)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brazilian</td>
<td>72/143 (50)</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USA</td>
<td>(34-70)</td>
<td>17</td>
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<tr>
<td></td>
<td></td>
<td>African</td>
<td>(4-25)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KSA</td>
<td>(8)</td>
<td>17</td>
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<tr>
<td></td>
<td></td>
<td>KSA</td>
<td>60/305 (20)</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sudan</td>
<td>30/261 (11)</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USA</td>
<td>4/47 (9)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Italy</td>
<td>(15)</td>
<td>50,51</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Jamaica</td>
<td>17/27 (63)</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UK</td>
<td>96/311 (31)</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KSA</td>
<td>55/95 (58)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Italy</td>
<td>60/170 (53)</td>
<td>56</td>
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<tr>
<td></td>
<td></td>
<td>India</td>
<td>5/80 (10)</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USA</td>
<td>11/42 (26)</td>
<td>34</td>
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<tr>
<td></td>
<td></td>
<td>USA</td>
<td>(50-70)</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>USA</td>
<td>15/36 (42)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nigeria</td>
<td>30/133 (23)</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USA</td>
<td>13/35 (37)</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KSA</td>
<td>50-85</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nigeria</td>
<td>23/140 (16%)</td>
<td>61</td>
</tr>
<tr>
<td>Sickle Cell Trait (Hb-SA) [0-29]</td>
<td>Children</td>
<td>Jamaican</td>
<td>00/25</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults</td>
<td>26/90 (29)</td>
<td>21</td>
</tr>
<tr>
<td>Sickle Cell Hemoglobin-C (Hb-SC) [3-23]</td>
<td>Both</td>
<td>USA</td>
<td>3/15 (20)</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>Jamaica</td>
<td>4/138 (3)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brazilian</td>
<td>10/44 (23)</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USA</td>
<td>3/15 (20)</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Jamaica</td>
<td>18/167 (11)</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>UK</td>
<td>24/95 (17)</td>
<td>17</td>
</tr>
</tbody>
</table>
1-Sickle Cell Disease (SCD): Most patients are asymptomatic. Symptomatic biliary tract disease is difficult to diagnose in patients with SCD, who frequently have acute abdominal pain, fever and jaundice, as symptoms of vaso-occlusive crisis. Distinguishing acute cholecystitis from the sickle hepatic crisis may be difficult because of their similar clinical presentations. Early recognition of this entity is essential to avoid life-threatening complications. The prevalence of pigmented gallstones in SCD directly related to the rate of hemolysis [17].

a- Sickle Cell Anaemia (Homozygous): Pigmented gallstones are seen in two third of patients, particularly in young children. Gallstones in children as young as 3-4 years of age found in about 70 percent of patients [18-23]. In a study of 509 adult patients with SCD, 48 percent of patients aged 18 to 47 years and 69 percent of those with more than 47 years of age had undergone cholecystectomy [24]. However, the frequency of gallstones in patients with sickle cell anaemia varies according to other studies [25-29].

b- Sickle Cell Trait (Heterozygous): The reported incidence of gallstones in patients with sickle cell trait is low (table 1) [20].

c- Hb-SC and Hb-S B-Thalassaemia syndrome: The risk of gallstones is low in patients with HbSC disease and HbSS-thalassemia [21].

d- Coinherited alpha thalassaemia causes decreased bilirubin level in patients with sickle cell disease. The incidence of gallstones and bilirubin levels strongly associated with the number of the UGT1A1 promoter (TA) repeats [22, 23].

2-Beta-Thalassaemias: Hemolysis and extra medullary erythropoiesis lead to the more prominent hepatomegaly in beta thalassaemias than in other causes of inherited haemolytic anaemia.

a- Beta-Thalassaemia Major. Two-thirds of patients have multiple, calcified bilirubin stones by the age of 15. However, cholecystitis or cholangitis are rare. Adult patients with beta-thalassaemia major have gallbladder dysmotility with delayed small bowel transit and autonomic dysfunction that together with hyperbilirubinemia contribute to the pathogenesis of pigment gallstones/sludge in beta-thalassaemia major [30].

b- Beta Thalassaemia Minor (Trait): Characterized by chronic ineffective erythropoiesis and variable levels of serum bilirubin. Thalassaemia minor represent a risk factor for gallstones, but the associated Gilbert mutation further increases this risk. Carriers of beta thalassaemia have significantly higher risk of gallstone formation than the normal population [31].

c- Beta-Thalassaemia Intermedia (Hb- E Beta-Thalassaemia): Chronic hyper bilirubinaemia, gallstones formation and gallbladder disease are unusually frequent in people with haemoglobin E - beta-thalassaemia.

This category is the most common of beta-thalassaemia of intermediate severity in the world and represents an important health problem for populations of the Indian subcontinent and Southeast Asia [32, 33].

3-Hereditary Spherocytosis (HS): Bilirubin stones found in 50 % of patients with HS between 30 and 50 years of age, even in those with very mild forms of the disease. Gallstones have reported during infancy, but they are uncommon in very young children. Pigmented gallstones form as early as 4-5 years old children, and at least 50 % of unsplenectomized patients ultimately form gallstones, although they may be asymptomatic. The incidence of gallstones is uncommon before age ten but is present in at least one-half of adults with more severe hemolytic disease [34]. The development of jaundice due to gallstones improves the hemolytic process and normalizes osmotic fragility [35]. The increased membrane surface area due to the abnormal plasma lipid profile normalizes the previously reduced surface area-to-volume ratio due to loss of membrane surface area in the spherocytes. The incidence of gallstones is increased further if the patient with HS co-inherits the genetic defect resulting in the diminished activity of the bilirubin conjugating enzyme uridine diphosphate-glucuronyltransferase (i.e., Gilbert syndrome). In a study of 102 children from southern Italy with mild to moderate HS, gallstones were found in 12, 26, and 48 percent of children who were normal, heterozygous, or homozygous for the Gilbert syndrome mutation, respectively. However, no significant difference in the age of onset of gallstones or the degree of hemolysis, as measured by average reticulocyte count [36].

4-Other chronic haemolytic anemias: The gallstones could also occur in patients with other inherited haemolytic anaemia such as Hb-H disease, autoimmune haemolytic anaemias, congenital dyserythropoietic anaemia, hereditary elliptocytosis, Southeast Asian Ovalocytosis and pyruvate kinase deficiency [8, 9]. Prevalence of gallstones in these blood disorders in not well known.

Management
Silent gallstones require no intervention. Laparoscopic cholecystectomy can be safely performed, but associated common bile duct stones first require endoscopic retrograde cholangiopancreato
graphy (ERCP) [37-39]. In hereditary spherocytosis, cholecystectomy is indicated for symptomatic gallstones with recurrent cholecystitis or biliary colic. Combined prophylactic splenectomy and cholecystectomy provide a substantial gain in life expectancy for young patients and adults with mild HS and gallstone [40, 41]. However, the use of concurrent splenectomy is controversial and considered on an individual basis, weighing the severity of haemolytic anemia versus the post-splenectomy risks [42-45]. Elective cholecystectomy considered in patients with sickle cell disorders and gallstones-related symptomatology [46]. After a decision is made to perform cholecystectomy, the gold standard surgical strategy is the laparoscopic cholecystectomy. Laparoscopic cholecystectomy is recommended because it associates with a shorter hospital stay and lower rates of postoperative complications. Prior to surgery, blood transfusion therapy is recommended and aimed to get the hemoglobin up to 100 g/l to prevent potentially life-threatening intra- and postoperative complications [47]. A multicenter, randomized trial compared observation with blood transfusion therapy no more than ten days prior to surgery [48]. In the latter multicenter study, a) out of the 70 enrolled patients, complications were more common in observation group than in transfusion group (39 versus 15 %), b) severe complications were more common in the observation group (30 versus 3 percent), c) acute chest syndrome occurred in nine of the participants in the observation group and one in the transfusion group, d) hemoglobin-S decreased to at least 30 % and total hemoglobin be increased at least 110 g/l to avoid sickling during the postoperative period. Blood transfusion considered for individuals with Hb-SS and Hb less than 90 g/l undergoing cholecystectomy. For individuals with Hb-SS or other types of SCD who have baseline hemoglobin greater than 90 g/l, partial exchange transfusion and adequate hydration are considered to avoid the development of hyperviscosity syndrome. Red blood cell pheresis designed to decrease the Hb-S level to <30 percent does not confer any advantage over simple blood transfusion therapy and preferably avoided, except under special circumstances [49-54]. During the surgery and the recovery period, hypotension, dehydration, hypoxia, hyperthermia and acidosis should be prevented [55]. Elective cholecystectomy is recommended for patients with hepato biliary symptoms and biliary sludge only [56]. Any symptomatic gallstone should be treated by cholecystectomy because the accelerated hemolysis in beta thalassaemia leads to the formation of gallstones. Since cholecystitis is life-threatening in any splenectomized patient, inspection of the gallbladder in any patient who is undergoing splenectomy recommended [31].

Conclusions and recommendations

1. Regular ultrasound examination for the presence of gallstones recommended in patients with inherited haemolytic anaemias, particularly those with additional risk factors.
2. Further studies for evaluating the reasons for the higher incidence of cholelithiasis in beta thalassaemia major, sickle cell anaemia compared to hereditary spherocytosis recommended.
3. Evaluation of the potential role of the solubility-changing mutations expressing low-solubility haemoglobin subunit in the red blood cells as an additional mechanism for the development of gallstones in patients with inherited haemolytic anaemias recommended.
4. The question whether gallstone disease is pertinent to the protein-aggregation or metabolism disorders requires toknow the sequence of proteolytic events in detail particularly in hematological diseases with unstable globins.
5. Additional studies both in laboratories and in the clinics will be necessary to appraise the role of haemoglobin degradation products (such as hemorphins) in physiology or pathology recommended.
6. The effect of coincidence of alpha thalassaemia decreasing bilirubin level in patients with sickle cell disease and beta thalassaemia require further evaluation.
7. The effect of the coincidence of uridine diphosphate-glucuronosyltransferase and ABCG8 gene mutation on the incidence of gallstones in other blood diseases (such as Hb-H disease, autoimmune haemolytic anaemia, congenital dyserythropoietic anaemia, here dietary elliptocytosis, Southeast Asian Ovalocytosis, glucose-6-phosphate dehydrogenase and pyruvate kinase deficiency) need to be formulated.

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CONFLICT OF INTERESTS

Declared None

REFERENCES


13