

Etiology Based Sickle Cell Disease Hepatopathy

Hassan Al-Jafar^{1*}, Jameela A. Alkhaldi², Salah Termos³

¹Hematology Department, Amiri Hospital, Ministry of Health, Kuwait City, Kuwait

²Gastroenterology Department, Amiri Hospital, Ministry of Health, Kuwait City, Kuwait

³Hepatobiliary & Transplant Surgery, Amiri Hospital, Ministry Of Health, Kuwait City, Kuwait

Email: *haj400004@gmail.com, *cbc9@hotmail.com, Jaf777@hotmail.com, Dr.Termos@hotmail.com

How to cite this paper: Al-Jafar, H., Alkhaldi, J.A. and Termos, S. (2020) Etiology Based Sickle Cell Disease Hepatopathy. *Open Journal of Gastroenterology*, **10**, 187-201.

<https://doi.org/10.4236/ojgas.2020.107019>

Received: June 6, 2020

Accepted: July 10, 2020

Published: July 13, 2020

Copyright © 2020 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

Sickle cell disease is an autosomal recessive disorder. The vas-occlusive crises lead to microinfarcts in the microvasculature in all organs, including the liver causing acute and chronic vascular complications in the form of ischemia, sequestration, and thrombosis, it also causes acute on top of chronic hepatic manifestations. Lifelong hemolytic anemia leads to precipitations of bile salts, bile pigments in intrahepatic, and extrahepatic bile ducts, which cause an important part of liver problems in sickle cell disease. Many other etiological factors could cause sickle cell disease hepatopathy. Liver problems in such patients could be fatal complications. Dealing with these complications based on the etiological factors provides a more accurate diagnosis for the overlapping liver manifestations in sickle cell disease, which means better treatment; it also simplifies this complicated medical issue. Sickle cell disease patients require periodic biochemistry and imaging studies to detect and treat hepatic complications as soon as possible.

Keywords

Sickle Cell Disease, Hepatopathy, Complication

1. Introduction

Sickle cell disease (SCD) is an autosomal recessive disorder caused by homozygosity in a sickle beta-globin gene mutation or double heterozygosity in the sickle gene and another mutation in a different hemoglobin variant or one of the numerous β -thalassemia mutations [1]. A genetic abnormality at the sixth position on the beta-globin chain due to a substitution of the amino acid valine for glutamic acid leads to the formation of hemoglobin S [2]. Valine is a hydrophobic amino acid, while glutamic acid is a hydrophilic amino acid. Therefore, this substitution creates a sticky patch at the valine hydrophobic spot, resulting

in the distortion of red blood cells, causing sickling and increased hemolysis [3]. SCD is widely prevalent in some countries. The USA estimated that 1 in 365 African-American infants have SCD, while 1 in 13 is born with sickle cell trait [4]. SCD is a chronic medical disorder characterized by severe anemia, painful crises, and organ dysfunction. Sickle cell hepatopathy is due to several etiological factors. Dealing with sickle cell hepatopathy from an etiology point of view provides an easier understanding and better diagnosis and treatment of SCD liver complications **Figure 1** [5]. SCD hepatopathy is an overlapping manifestation as more than one complication could exist at the same time. In this study, the etiology factors of SCD hepatopathy classified based on hepatic vasculature complications, intrahepatic and extrahepatic bile ducts obstructions, hepatic infections, iron overload, drug-induced liver disease, and other etiological factors related to SCD as liver cirrhosis, post-liver transplant, surgical trauma, nutritional deficiencies and autoimmune liver diseases related to sickle cell disease.

2. Hematology and Vasculature Complications

2.1. Hemolytic Benign Hyperbilirubinemia (HBH)

It is caused by hemolytic anemia. The HBH is associated with an increase of red blood cells destruction in the hemolytic episodes, which are spontaneously reversible status [6]. Most bilirubin is produced when hemoglobin is broken down into unconjugated bilirubin. Unconjugated bilirubin is to bind albumin in the blood to transport to the liver, where it's taken up by the hepatocytes and conjugated with glucuronic acid to make it water-soluble. The conjugated bilirubin is excreted in the bile to the duodenum. In the intestine, the bacteria metabolize bilirubin to form urobilinogen. This urobilinogen is eliminated in the feces, and some

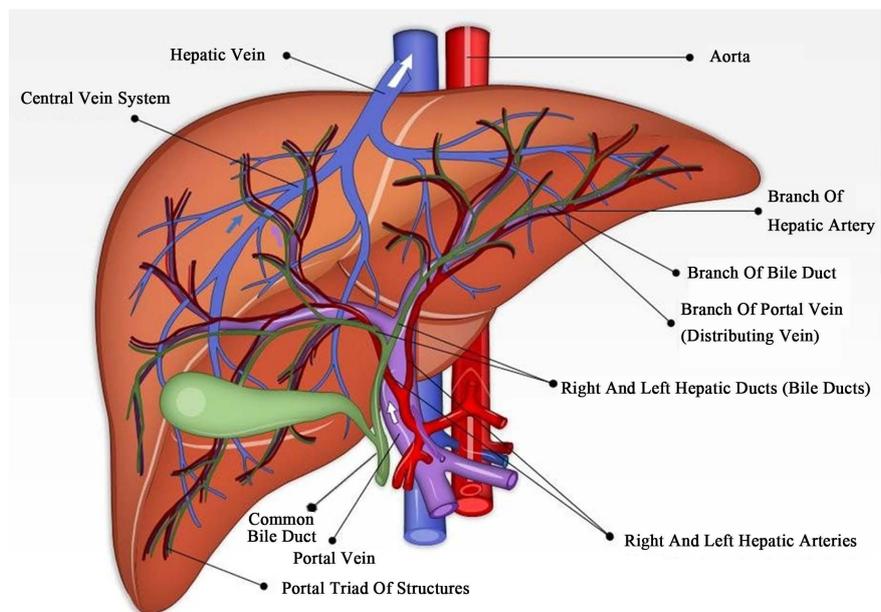


Figure 1. Internal anatomy of the liver [5].

are reabsorbed, extracted by hepatocytes, reprocessed, and re-excreted in bile [7]. Unconjugated hyperbilirubinemia is most often caused by one or more of the following reasons, increased production, decreased hepatic uptake, decreased conjugation [8]. It also could be caused by an underlying chronic hemolytic crisis [9]. Biochemical abnormalities in BH usually include significant increase hyperbilirubinemia, which can be as high as 410 $\mu\text{mol/L}$ [10]. Elevation in indirect bilirubin, LDH, and AST without other evidence of liver disease is found in 72% of patients with SCA, which is related to the hemolysis [11]. In HBH, we assume the liver is within normal, but the hyperbilirubinemia is due to an increase in the hemolytic process.

2.2. Sickle Ischemic Hepatic Crises (SIHC)

The first mechanism for this entity is believed to be due to sickled erythrocytes that causing a mild sinusoidal obstruction. This obstruction can cause transient liver ischemia and, in severe cases, can lead to infarction. On histology, sickle cell aggregates are observed in sinusoidal spaces. Depending on the severity of the vaso-occlusive crisis, kupffer cell hypertrophy, and in most severe cases, severe centrilobular necrosis can also be observed [12]. SIHC is a clinical syndrome that typically presents with acute right upper quadrant pain, jaundice, low-grade fever, nausea, and tender hepatomegaly. The serum AST and ALT levels are usually less than 300 IU/L, and total bilirubin rarely exceeds 256 $\mu\text{mol/L}$ [13]. It is usually self-limited and resolves with analgesia and intravenous fluid administration. In more severe cases, blood exchange transfusions may be necessary. The prevalence of SHC is not well documented but may occur in up to 10% of patients with SCD [14]. Diagnosis is often challenging because patients typically have other factors contributing to liver dysfunction, such as transfusion-related iron overload, gallstone disease, graft rejection, and recurrent hepatitis C infection [15].

2.3. Sickle Severe Ischemic Hepatic Crises (SSIHC)

It is a distinct clinical entity, but some consider it a severe form of SIHC. It results from the severe obstruction of liver sinusoids leading to stasis, hypoxia, and intracanalicular cholestasis secondary to the ballooning of the hepatocytes. Clinically, it resembles an acute hepatic crisis, but the main differentiating points are the associated extreme hyperbilirubinemia, coagulopathy, and acute hepatic failure. Early recognition of this potentially fatal condition is crucial as it ultimately leads to liver failure, encephalopathy, and renal impairment [16]. The diagnosis of SSIHC is based on clinical and laboratory evidence of non-obstructive cholestasis, moderately elevated hepatic enzymes, and an enlarged and painful liver. SSIHC including marked conjugated hyperbilirubinemia, right upper quadrant pain, enlarged liver, and a coagulation disorder but only moderately elevated liver enzymes [17]. SSIHC can be subdivided into mild (average direct bilirubin, 471 $\mu\text{mol/L}$) and severe disease, average direct bilirubin, 1313 $\mu\text{mol/L}$, or presence of a change in mental status or coagulation disorder, with death rates of

4% and 64% respectively [18]. The histological consequences of intrahepatic sickling include the impaction of hepatic sinusoids with sickled red blood cells, patchy areas of hepatocellular necrosis, engorgement of Kupffer cells, and bile stasis [19]. There are no randomized clinical trials with enough evidence to prove the efficacy of therapeutic measures [20]. However, the prognosis of SSIHC improved significantly with the advent of exchange blood transfusions. The incidence is higher in children. Adults tend to experience more aggressive disease course, with a mortality rate as high as 50% [21].

2.4. Sickle Hepatic Sequestration (SHS)

Sequestration of red blood cells is a known complication of SCD, it is more commonly observed in the lungs and spleen [22]. The SHS crisis is caused by the obstruction of the blood flow from the liver sinusoids by the sickled red blood cells leading to the compression of the bile ducts [23]. In severe cases, this leads to stagnant of the blood within the liver, causing acute hepatic enlargement. It is associated with a rapid drop in hemoglobin and hematocrit levels and an increase in reticulocyte count and bilirubin levels [24]. The liver enzymes mildly elevated, and hyperbilirubinemia is that of the conjugated fraction. Once diagnosed and treated with hydration and blood transfusion, it behaves like splenic sequestration with regression of the hepatic size and increase in hemoglobin level. Recurrence is common, and the form of chronic SHS has also been reported [16].

2.5. Sickle Hepatic Infarction (SHI)

A rare condition because of the liver's dual blood supply by the hepatic artery and portal vein. SHI can occur when blood flow is occluded in both the hepatic artery and the portal vein, but most cases are due to acute portal vein obstructions. SHI was mainly seen after liver transplantation or hepatobiliary surgery. SHI has been observed in 34% of SCD autopsies. In half of these cases, the associated cause is infarction as cardiac dysfunction or sepsis existed. The resulting high blood viscosity contributes to a predisposition to infarction despite the dual blood supply of the liver [25]. The reported incidence of hepatic crises is about 10% in adults with SCD [26]. SHI could either be asymptomatic or cause right upper quadrant pain, fever, nausea, vomiting, and jaundice. Leukocytosis and high aminotransferase levels are common [27].

2.6. Sickle Budd-Chiari Syndrome (SBS)

Is an uncommon problem that results from blood clotting in the veins flowing out of the liver or hepatic veins. The high pressure of the blood in these veins leads to an enlarged liver and accumulation of ascites. The main symptoms include pain in the upper right portion of the abdomen and a buildup of fluid in the abdomen. Blood disorders, such as polycythemia vera and SCD, are the most common causes of SBS [28]. The SBS with both hepatic vein thrombosis and inferior vena cava thrombosis has been described in patients with SCD. Extensive

thrombosis involving the hepatic, portal, superior mesenteric, and splenic veins has also been described in SCD [29]. The presentation may be acute or chronic. The acute form results from an acute thrombosis of the main hepatic veins or the inferior vena cava. The classic acute presentation is characterized by a rapid onset of ascites, hepatomegaly, and abdominal pain, although it is nonspecific. The chronic form is related to fibrosis of the intrahepatic veins, presumably related to inflammation. In a few cases, there may also be unusual swelling due to abnormal accumulation of fluid within the tissues of the legs. In some cases, affected individuals may have liver cirrhosis following the development of SBS [30].

3. Biliary Tract Complications

Sickle Cholelithiasis (SCh) and Sickle Choledocholithiasis (SChd)

Gallstone disease SCh is fairly common in patients with homozygous SCD, with an incidence of 26% - 58% in patients aged 10 - 65 [31]. The gallstones form in the gallbladder but may exit into the bile ducts choledocholithiasis. Hence, this is a complication particularly, when stones obstruct the common bile duct and thereby impede the flow of bile from the liver is to the intestine [32]. Pressure rises, resulting in the elevation of liver enzymes, jaundice, and sometimes fever, cholangitis, sepsis, and cholangiohepatitis [33]. In SCh, most patients with gallstones are asymptomatic, or the patient may experience intermittent abdominal pain related to fatty food. Frequently, it goes unnoticed except when the patient presents with acute cholecystitis or SChd. Acute cholecystitis symptoms are abdominal pain, nausea, vomiting, fever with or without jaundice. Acute cholecystitis should be differentiated from the sickle cell hepatic crisis. Imaging, as well as recognition of the pattern of acute hepatic crisis in such cases, can help to differentiate these two entities. SChd incidence is 19% - 26%; it could be symptomatic or asymptomatic [34]. However, if significant obstruction persists, they present with right upper quadrant or epigastric pain and jaundice.

4. Infection

Patients with SCD are a high-risk group for hepatitis virus infections due to the need for blood transfusions and surgical interventions resulting from complications [35]. Although blood banks worldwide run screening programs for various pathogens, the risk of infection with viruses still exists [36]. Hence, the overall prevalence of hepatitis decreases with improvements in the socioeconomic status, the use of new generation assays in blood banks for the detection of hepatitis C viral (HCV) antibodies, and vaccination programs against hepatitis B viral (HBV). It is shown that the prevalence of HCV infections in patients with SCD was significantly higher than that observed in otherwise healthy individuals [37]. HCV infection characterized by a prolonged period in which there are no symptoms [38]. In the current COVID-19 virus Pandemic the patients, who are otherwise healthy or have chronic disorders such as SCD patients may be asso-

ciated with macrophage activation syndrome, a hyperinflammatory syndrome characterized by a cytokine storm and multi-organ failure [39]. However, systemic viral infections are often associated with transient elevations of transaminases. These may also be the case in patients with COVID-19, where liver failure has not been specifically reported, even in patients with the most severe and fatal course of the disease [40]. Between patients with cirrhosis and COVID-19, are they at increased risk of decompensation or development of acute-on-chronic liver failure, as has been shown for influenza infection, that remains to be determined [41].

5. Iron Overload

Iron overload or secondary hemochromatosis is one of SCD complications due to recurrent blood transfusions because of chronic hemolytic anemia; each pint of blood contains 250 mg of iron. Iron overload is defined as excess iron stores in the body; hence, excess iron is deposited in organs throughout the body. The most notable organs with iron deposition are the liver, heart, and endocrine glands [42]. The microscopic examination of the involved tissues reveals iron deposition. A liver biopsy can show hemosiderosis on iron staining as well as cirrhosis of liver disease is advanced [43]. When signs and symptoms occur, they are generally related to specific organ involvement. These include chronic fatigue, arthralgia, abdominal pain, hepatomegaly, irregular heart rhythm, hypogonadism, decreased libido, elevated blood glucose levels, hyperpigmentation (bronze skin), and depression [44]. Patients with iron overload are asymptomatic in three out of four cases. If transfusion is given without chelation, portal fibrosis can develop as early as two years after transfusion. Fibrosis was found in one-third of patients.

The long-term consequences of uncontrolled liver iron are cirrhosis. Post-mortem studies have found cirrhosis in 11% of all patients and in about 50% of patients who died with severe liver siderosis [45]. In such adult patients, the risk of liver cancer exists, and it would be advisable to perform yearly abdominal ultrasound and alpha-fetoprotein [46].

6. Drug Induced

Drug-induced liver injury (DILI) is common, and nearly all classes of medications can cause liver disease. Most cases of DILI are benign and improve after drug withdrawal. It is important to recognize and remove the offending agent as quickly as possible to prevent the progression of chronic liver disease and liver failure. DILI can present with a wide range of acute and chronic liver diseases, including acute hepatitis, cholestasis, or a mixed pattern [47]. Some drugs in use in SCD treatment documented to cause DILI as Hydroxyurea, which is to stimulate fetal hemoglobin production in SCD. Hydroxyurea has been implicated in cases of clinically apparent acute liver injury with jaundice [48]. Deferasirox, which also frequently used as a chelating agent in SCD, may change liver enzymes parameters, despite being rare, more serious complications such as liver

failure [49]. L-glutamine recently approved by the FDA as an SCD treatment agent that it possible has a side effect on the liver [50]. Antibiotics like amoxicillin-clavulanate are the most frequent cause of idiosyncratic DILI [51], ceftriaxone is also a commonly used antibiotic and has been associated with reversible biliary sludge, pseudolithiasis, and cholestasis, [52] also some pain killers that frequently needed for SCD patients can cause DILI as acetaminophen, nonsteroidal anti-inflammatory drugs, naproxen, ibuprofen, and anabolic steroids [53] [54].

7. Cirrhosis

Liver cirrhosis in SCD usually related to chronic hepatitis B or C infection or to iron overload resulting from the many transfusions received by these patients in their lifetime. Approximately 15% - 30% of patients with SCD have cirrhosis at autopsy [55]. Cirrhosis is slow and moderate in its development. It's usually well advanced before the symptoms are noticeable enough to cause an alarm. The early symptoms may be weakness and weight loss [56]. Cirrhosis itself is already a late stage of liver damage. These inflammations are not treated; it can lead to scarring (fibrosis). If the fibrosis of the liver is not treated, this results in cirrhosis. Stage 1 cirrhosis involves some scarring of the liver, with few symptoms. This stage is considered compensated cirrhosis, where there are no complications. Stage 2 cirrhosis includes worsening portal hypertension and the development of varices. Stage 3 cirrhosis involves the development of ascites and advanced liver scarring. This stage marks decompensated cirrhosis, with serious complications and possible liver failure. Stage 4 cirrhosis can be life-threatening, and people have developed end-stage liver disease (ESLD), which is fatal without a transplant [57].

8. Post-Liver Transplant

SCD patients with ESLD need liver transplantation. The recipients of liver transplant are at high risk of suffering from multiple and severe complications. Graft related complications are biliary, surgical, systemic, infectious, cardiovascular, pulmonary, and renal which are associated with increased risk of recipient mortality or graft loss [58] SCD patients are at high risk of liver transplant complications, including drug toxicity, graft-versus-host disease, and graft rejection due to prior tissue damage, and inflammation [59]. Patients commonly manifest symptoms as fever, rash, and diarrhea in the post-transplantation state; these symptoms are usually and correctly attributed to the drug toxicity or infectious processes. Well-known side effects of commonly used immunosuppressive drugs include gastrointestinal intolerance and cytopenias [60]. Post-transplant rejection related to the vascular anastomosis, hepatic arterial thrombosis: most common vascular complication occurring in 2% - 12% of transplants [61], hepatic abscess, biliary ischemia, stricture [62], arterial pseudoaneurysm, portal vein thrombosis, stenosis, hepatic vein thrombosis, inferior vena cava thrombosis, related to the biliary anastomosis, bile leak, biliary, infection, ischemia, cal-

culus, cholangitis, and sepsis. Post-liver transplant, many complications are should be expected. In SCD, it could be more severe.

9. Biloma

It is a rare abnormal accumulation of intrahepatic or extrahepatic bile [63]. The causes of biloma include trauma to the liver, abdominal surgery, endoscopic procedures, and percutaneous catheter drainage. Currently, the term biloma is generally used to describe intrahepatic or intraperitoneal focal biliary stasis [64]. In SCD, patients develop spontaneous biloma presenting with acute abdominal pain, jaundice, and fever. Pneumobilia is a gas collection within the biliary system due to an abnormal connection between the biliary tree and adjacent organs, particularly the gastrointestinal tract. Although hepatobiliary complications are common in SCD, the diagnosis is suspected based on the clinical history of recent cholecystectomy or abdominal trauma, location of the lesion, ultrasound, and computed tomography (CT), magnetic resonance (MR), and cholangiopancreatography. Gallbladder scintigraphy with technetium-99 may help differentiate biloma from hematoma or a liver abscess [65]. Endoscopic retrograde cholangiography may provide not only further diagnostic confirmation but also a therapeutic option, allowing the decompression of the bile duct and the biliary drainage of the fluid and gas collection [66].

10. Nutritional Bioelements Deficiency

Early findings suggest that zinc deficiency in SCD could lead to hyperammone-mia. This has been attributed to chronic hemolysis, increased demand, utilization, and secondary loss of zinc in the urine [34]. In addition, zinc deficiency has been suggested as a strong factor when hepatic failure is observed in SCD [67]. Selenium deficiency increases oxidative stress in the red blood cells of SCD patients, as selenium is an antioxidant agent protecting hemoglobin from reactive oxygen species (ROS) and has been reported to be lower in the red blood cells in SCD [68]. Vitamin D is lower in patients with SCD; this finding hypothesizes that metabolic demands have reduced the capacity of the liver to synthesize vitamin D binding protein [69]. Vitamin A deficiency is common in cholecystectomy, which is common in SCD because of decreased bile acid secretion, which causes fat and fat-soluble vitamin malabsorption [70]. As liver disease progresses, vitamin A deficiency becomes more prevalent [71]. Vitamin B12/ Cobalamin It has been suggested that SCD poses a risk for cobalamin deficiency because of the increased demand from a high turnover of red blood cells. [72]. Previous study published data confirm that serum cobalamin is significantly lower in SCD. It is present in 6.9% of SCD patients [73].

11. Autoimmune Liver Disease (AILD)

Is a chronic disease of the liver that occurs when the body's immune system attacks the liver cells, causing the liver to be inflamed. Common initial symptoms

include fatigue, muscle aches, signs of liver inflammation, including fever, jaundice, and abdominal pain at the right upper quadrant. Individuals having autoimmune hepatitis often have no initial symptoms, and the disease is detected by abnormal liver function tests [74]. Patients with AILD, 60% of them may mimic viral hepatitis in clinical manifestations, but without the serologic evidence of viral infection. The disease is strongly associated with the anti-smooth muscle autoantibodies, and currently, no evidence as to any specific cause [75]. AILD is not rare in patients with SCD [76]. However, a study by Chuang *et al.* 1997 reported three cases AILD and SCD in children. Maher *et al.* study the serological markers for autoimmune hepatitis were positive in two female patients; clinically, both had jaundice and hepatomegaly, the liver biopsy revealed signs of chronic active hepatitis with cirrhosis associated with dilated sinusoids lined by lymphocytes and hyperplastic Kupffer cells. Perisinusoidal fibrosis was present, whether a pathophysiological link exists between SCD and autoimmune hepatitis remains to be determined [77]. In the association between AILD and SCD, the noteworthy 17% of SCD patients in a cohort of 77 children showed serology and/or histologic signs of AILD affecting mainly female patients and responding well to immunosuppression [76].

12. Conclusion

Sickle cell disease hepatopathy is one of the most common complications of sickle cell disease the treating doctors face on a daily basis. A sickle cell hepatopathy is a group of disorders from the different etiological background with similar overlapping clinical manifestations. The etiological classification provides more distinction to the type of the hepatopathy cause rather than the classification based on the chronicity of the hepatopathy. The etiology classification makes the diagnosis, treatment, prognosis, and follow up of sickle cell patients with hepatopathy handy and more accurate that will reflect on the confidence in treatment in the proper manner. This study is part of our project concern about the clinical classification of sickle cell disease according to the systemic complications.

Acknowledgements

This research work done under the “Classification of sickle cell disease systemic complication” with Ministry of Health ethical approval number DVR/906, and funded “Partially” by Kuwait Foundation for the advancement of science under code: P116-13MM-01, our grateful for KFAS support.

Conflicts of Interest

The authors have no conflict of interest in this study.

References

- [1] Cordovil, K. (2018) Sickle Cell Disease: A Genetic Disorder of Beta-Globin. In:

Thalassemia and Other Hemolytic Anemias, IntechOpen, Isam Al-Zwaini.

<https://doi.org/10.5772/intechopen.74778>

- [2] Jensen, F.B. (2009) The Dual Roles of Red Blood Cells in Tissue Oxygen Delivery: Oxygen Carriers and Regulators of Local Blood Flow. *Journal of Experimental Biology*, **212**, 3387-3393. <https://doi.org/10.1242/jeb.023697>
- [3] Roy, S. and Ganguly, S. (2013) Sickle Cell Anemia, an Autosomal Recessive Disorder: A Review. *International Journal of Molecular Genetics*, **3**, 63-67. <http://www.ripublication.com/ijmg.htm>
- [4] Hassel, K.L. (2010) Population Estimates of Sickle Cell Disease in the U.S. *American Journal of Preventive Medicine*, **38**, S512-S521. <https://doi.org/10.1016/j.amepre.2009.12.022>
- [5] Anatomy of the Liver. <https://www.slideteam.net/catalog/product/gallery/id/35454/image/262076>
- [6] Roche, S.P. and Kobos, R. (2004) Jaundice in the Adult Patient. *American Family Physician*, **69**, 299-304.
- [7] Kuntz, E. (2008) *Hepatology: Textbook and Atlas*. Springer, Berlin, 38.
- [8] Singh, A. and Jialal, I. (2019) Unconjugated Hyperbilirubinemia. StatPearls Publishing, Treasure Island. <https://www.ncbi.nlm.nih.gov/books/NBK549796>
- [9] Fabris, L., Cadamuro, M. and Okolicsanyi, L. (2009) The Patient Presenting with Isolated Hyperbilirubinemia. *Digestive and Liver Disease*, **41**, 375-381. <https://doi.org/10.1016/j.dld.2008.11.006>
- [10] Shah, R., Taborda, C. and Chawla, S. (2017) Acute and Chronic Hepatobiliary Manifestations of Sickle Cell Disease: A Review. *World Journal of Gastrointestinal Pathophysiology*, **8**, 108-116. <https://doi.org/10.4291/wjgp.v8.i3.108>
- [11] Johnson, C.S., Omata, M. and Tong, M.J. (1985) Liver Involvement in Sickle Cell Disease. *Medicine*, **64**, 349-356. <https://doi.org/10.1097/00005792-198509000-00007>
- [12] Sheehy, T.W. (1977) Sickle Cell Hepatopathy. *Southern Medical Journal*, **70**, 533-538. <https://doi.org/10.1097/00007611-197705000-00008>
- [13] Banerjee, S., Owen, C. and Chopra, S. (2001) Sickle Cell Hepatopathy. *Hepatology*, **33**, 1021-1028. <https://doi.org/10.1053/jhep.2001.24114>
- [14] Gardner, K., Suddle, A., Kane, P., *et al.* (2014) How We Treat Sickle Hepatopathy and Liver Transplantation in Adults. *Blood*, **123**, 2302-2307. <https://doi.org/10.1182/blood-2013-12-542076>
- [15] Gillis, J.H., Satapathy, S.K., Parsa, L., Sylvestre, P.B. and Dbouk, N. (2015) Acute Sickle Hepatic Crisis after Liver Transplantation in a Patient with Hb SC Disease. *Case Reports in Transplantation*, **2015**, Article ID: 761740. <https://doi.org/10.1155/2015/761740>
- [16] Jeng, M.R., Rieman, M.D., Naidu, P.E., Kaste, S.C., Jenkins, J.J., Serjeant, G. and Wang, W.C. (2003) Resolution of Chronic Hepatic Sequestration in a Patient with Homozygous Sickle Cell Disease Receiving Hydroxyurea. *Journal of Pediatric Hematology/Oncology*, **25**, 257-260. <https://doi.org/10.1097/00043426-200303000-00015>
- [17] Guimarães, J.A. and Silva, L.C.D.S. (2017) Sickle Cell Intrahepatic Cholestasis Unresponsive to Exchange Blood Transfusion: A Case Report. *Revista Brasileira de Hematologia e Hemoterapia*, **39**, 163-166. <https://doi.org/10.1016/j.bjhh.2017.02.006>
- [18] Ahn, H., Li, C.-S. and Wang, W. (2005) Sickle Cell Hepatopathy: Clinical Presentation, Treatment, and Outcome in Pediatric and Adult Patients. *Pediatric Blood &*

- Cancer*, **45**, 184-190. <https://doi.org/10.1002/pbc.20317>
- [19] Teixeira, A.L., Viana, M.B., Roquete, M.L. and Toppa, N.H. (2002) Sick Cell Disease: A Clinical and Histopathologic Study of the Liver in Living Children. *Journal of Pediatric Hematology/Oncology*, **24**, 125-129. <https://doi.org/10.1097/00043426-200202000-00013>
- [20] Porzolt, F., Rocha, N.G., Toledo-Arruda, A.C., et al. (2016) Efficacy and Effectiveness Trials Have Different Goals, Use Different Tools, and Generate Different Messages. *Pragmatic and Observational Research*, **6**, 47-54.
- [21] Papafragkakis, H., Ona, M.A., Changela, K., et al. (2014) Acute Liver Function De-compensation in a Patient with Sick Cell Disease Managed with Exchange Transfusion and Endoscopic Retrograde Cholangiography. *Therapeutic Advances in Gastroenterology*, **7**, 217-223. <https://doi.org/10.1177/1756283X14530781>
- [22] Allali, S., de Montalembert, M., Brousse, V., et al. (2019) Hepatobiliary Complications in Children with Sick Cell Disease: A Retrospective Review of Medical Records from 616 Patients. *Journal of Clinical Medicine*, **8**, 1481. <https://doi.org/10.3390/jcm8091481>
- [23] Koullapis, N., Kouroupi, I.G. and Dourakis, S.P. (2005) Hepatobiliary Manifestations of Sick Cell Disease. *Haema*, **8**, 393-404.
- [24] Edwards, C.Q. (2002) Anemia and the Liver. Hepatobiliary Manifestations of Anemia. *Clinical Liver Disease*, **6**, 891-907. [https://doi.org/10.1016/S1089-3261\(02\)00050-8](https://doi.org/10.1016/S1089-3261(02)00050-8)
- [25] Bauer, T.W., Moore, G.W. and Hutchins, G.M. (1980) The Liver in Sick Cell Disease. A Clinicopathologic Study of 70 Patients. *The American Journal of Medicine*, **69**, 833-837. [https://doi.org/10.1016/S0002-9343\(80\)80008-8](https://doi.org/10.1016/S0002-9343(80)80008-8)
- [26] Johnson, C.S., Omata, M., Tong, M.J., Simmons Jr., J.F., Weiner, J. and Tatter, D. (1985) Liver Involvement in Sick Cell Disease. *Medicine (Baltimore)*, **64**, 349-356. <http://doi.org/10.1097/00005792-198509000-00007>
- [27] Giannini, E.G., Testa, R. and Savarino, V. (2005) Liver Enzyme Alteration: A Guide for Clinicians. *CMAJ*, **172**, 367-379. <https://doi.org/10.1503/cmaj.1040752>
- [28] Aydinli, M. and Bayraktar, Y. (2007) Budd-Chiari Syndrome: Etiology, Pathogenesis and Diagnosis. *World Journal of Gastroenterology*, **13**, 2693-2696. <https://doi.org/10.3748/wjg.v13.i19.2693>
- [29] Arnold, K.E., Char, G. and Serjeant, G.R. (1993) Portal Vein Thrombosis in a Child with Homozygous Sick-Cell Disease. *West Indian Medical Journal*, **42**, 27-28.
- [30] Zhou, H., et al. (2000) Multiple Macroregenerative Nodules in Liver Cirrhosis Due to Budd-Chiari Syndrome. Case Reports and Review of the Literature. *Hepatogastroenterology*, **47**, 522-527.
- [31] Bond, L.R., Hatty, S.R., Horn, M.E., Dick, M., Meire, H.B. and Bellingham, A.J. (1987) Gallstones in Sick Cell Disease in the United Kingdom. *British Medical Journal*, **295**, 234-236. <https://doi.org/10.1136/bmj.295.6592.234>
- [32] Kimiko Suzue Department of Pathology—Presentation Transcript. <http://slideplayer.com/slide/9486797>
- [33] Tanaja, J. and Meer, J.M. (2019) Cholelithiasis. StatPearls Publishing, Treasure Island.
- [34] Khan, Steven, J.T. and Dinko, N. (2009) Zinc Deficiency Causing Hyperammonemia and Encephalopathy in a Sick Cell Patient. *Chest*, **136**, 37S-7d. https://doi.org/10.1378/chest.136.4_MeetingAbstracts.37S-d
- [35] Nouraie, M., Nekhai, S. and Gordeuk, V.R. (2012) Sick Cell Disease Is Associated

- with Decreased HIV But Higher HBV and HCV Comorbidities in US Hospital Discharge Records: A Cross-Sectional Study. *Sexually Transmitted Infections*, **88**, 528-533. <https://doi.org/10.1136/sextrans-2011-050459>
- [36] Allain, J.P., Bianco, C., Blajchman, M.A., *et al.* (2005) Protecting the Blood Supply from Emerging Pathogens: The Role of Pathogen Inactivation. *Transfusion Medicine Reviews*, **19**, 110-126. <https://doi.org/10.1016/j.tmr.2004.11.005>
- [37] Al-Suliman, A.M., Busaobiuah, J., Al-Baqshi, M., Qadiaub, K., Mohammad, B., Homrany, H., Aljassam, A. and Khan, S.A. (2013) Prevalence of Hepatitis B and C in Adult Sickle Cell Disease Patients in the Eastern Province of Saudi Arabia. *Journal of Applied Hematology*, **4**, 33-35.
- [38] Hassan, M., *et al.* (2003) HCV in Sickle Cell Disease. *Journal of the National Medical Association*, **95**, 864-874.
- [39] Boettler, T., Newsome, P.N., Mondelli, M.U., Maticic, M., Cordero, E., Cornberg, M. and Berg, T. (2020) Care of Patients with Liver Disease during the COVID-19 Pandemic: EASL-ESCMID Position Paper. JHEP Reports. <https://doi.org/10.1016/j.jhepr.2020.100113>
- [40] Guan, W.-J., Ni, Z.-Y., Hu, Y., Liang, W.-H., Ou, C.-Q., He, J.-X., *et al.* (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*, **382**, 1708-1720. <https://doi.org/10.1101/2020.02.06.20020974>
- [41] Schütte, A., Ciesek, S., Wedemeyer, H. and Lange, C.M. (2019) Influenza Virus Infection as Precipitating Event of Acute-on-Chronic Liver Failure. *Journal of Hepatology*, **70**, 797-799. <https://doi.org/10.1016/j.jhep.2018.11.015>
- [42] Powell, L.W., Subramaniam, V.N. and Yapp, T.R. (2000) Haemochromatosis in the New Millennium. *Journal of Hepatology*, **32**, 48-62. [https://doi.org/10.1016/S0168-8278\(00\)80415-8](https://doi.org/10.1016/S0168-8278(00)80415-8)
- [43] McDowell, L.A. and Sticco, K.L. (2020) Iron Overload. StatPearls Publishing, Treasure Island. <https://www.ncbi.nlm.nih.gov/books/NBK526131>
- [44] McLaren, G.D., McLaren, C.E., Adams, P.C., Barton, J.C., Reboussin, D.M., Gordeuk, V.R., Acton, R.T., Harris, E.L., Speechley, M.R., Sholinsky, P., Dawkins, F.W., Snively, B.M., Vogt, T.M. and Eckfeldt, J.H. (2008) Hemochromatosis and Iron Overload Screen (HEIRS) Study Research Investigators. Clinical Manifestations of Hemochromatosis in HFE C282Y Homozygotes Identified by Screening. *Canadian Journal of Gastroenterology*, **22**, 923-930. <https://doi.org/10.1155/2008/907356>
- [45] Darbari, D.S., Kple-Faget, P., Kwagyan, J., Rana, S., Gordeuk, V.R. and Castro, O. (2006) Circumstances of Death in Adult Sickle Cell Disease Patients. *American Journal of Hematology*, **81**, 858-863. <https://doi.org/10.1002/ajh.20685>
- [46] Porter, J. and Garbowski, M. (2013) Consequences and Management of Iron Overload in Sickle Cell Disease. *Hematology—American Society of Hematology Education Program*, **2013**, 447-456. <https://doi.org/10.1182/asheducation-2013.1.447>
- [47] Andrade, R.J. and Robles-Díaz, M. (2020) Diagnostic and Prognostic Assessment of Suspected Drug-Induced Liver Injury in Clinical Practice. *Liver International*, **40**, 6-17. <https://doi.org/10.1111/liv.14271>
- [48] (2012) Hydroxyurea LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda. <https://www.ncbi.nlm.nih.gov/books/NBK548724>
- [49] (2012) Deferasirox LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda. <https://www.ncbi.nlm.nih.gov/books/NBK548039>
- [50] Hatami, B., Saffaei, A., Jamali, F. and Abbasinazari, M. (2020) Glutamine Powd-

er-Induced Hepatotoxicity: It Is Time to Understand the Side Effects of Sports Nutritional Supplements. *Gastroenterology and Hepatology from Bed to Bench*, **13**, 86-89.

- [51] deLemos, A.S., Ghabril, M., Rockey, D.C., et al. (2016) Amoxicillin-Clavulanate-Induced Liver Injury. *Digestive Diseases and Sciences*, **61**, 2406-2416. <https://doi.org/10.1007/s10620-016-4121-6>
- [52] Andrade, R.J., Robles, M. and Lucena, M.I. (2009) Re-Challenge in Drug-Induced Liver Injury: The Attractive Hazard. *Expert Opinion on Drug Safety*, **8**, 709-714. <https://doi.org/10.1517/14740330903397378>
- [53] MedlinePlus (2014) Drug-Induced Hepatitis: MedlinePlus Medical Encyclopedia.
- [54] Chalasani, N.P., Hayashi, P.H., Bonkovsky, H.L., et al. (2014) ACG Clinical Guideline: The Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. *American Journal of Gastroenterology*, **109**, 950-966. <https://doi.org/10.1038/ajg.2014.131>
- [55] Lerut, J.P., Clayes, N., Laterre, P.F., Lavenne-Pardonge, E., Ciccarelli, O., Cavallaro, S., Palazzo, U., Renda, D., Rigano, P. and Maggio, A. (1999) Hepatic Sickling: An Unusual Case of Liver Allograft Dysfunction. *Transplantation*, **67**, 65-68. <https://doi.org/10.1097/00007890-199901150-00010>
- [56] Gee, Y., Geong, Kang, S., Lee, C. and Burgio, A. (2019) An Updated Review on the Epidemiology, Pathophysiology, Etiology, and Diagnosis of Liver Cirrhosis.
- [57] Cunha, J.P. and Marks, J.W. Cirrhosis (Liver). https://www.medicinenet.com/cirrhosis/article.htm#what_is_sofosbuvir_and_velpat_asvir_what_is_sofosbuvir_and_velpatasvir_used_for
- [58] Daugaard, T.R., Pommergaard, H.-C., Rostved, A.A. and Rasmussen, A. (2018) Postoperative Complications as a Predictor for Survival after Liver Transplantation—Proposition of a Prognostic Score. *International Hepato-Pancreato-Biliary*, **20**, 815-822. <https://doi.org/10.1016/j.hpb.2018.03.001>
- [59] Ozdogu, H., Boga, C., Yeral, M., et al. (2018) Allogenic Peripheral Stem Cell Transplantation from HLA-Matched Related Donors for Adult Sickle Cell Disease: Remarkable Outcomes from a Single-Center Trial. *Bone Marrow Transplant*, **53**, 880-890. <https://doi.org/10.1038/s41409-018-0111-y>
- [60] Perri, R., Assi, M., Talwalkar, J., Heimbach, J., Hogan, W., Moore, S.B. and Rosen, C.B. (2007) Graft vs. Host Disease after Liver Transplantation: A New Approach Is Needed. *Liver Transplantation*, **13**, 1092-1099. <https://doi.org/10.1002/lt.21203>
- [61] Langnas, A.N., Marujo, W., Stratta, R.J., Wood, R.P. and Shaw, B.W. (1991) Vascular Complications after Orthotopic Liver Transplantation. *The American Journal of Surgery*, **161**, 76-83. [https://doi.org/10.1016/0002-9610\(91\)90364-J](https://doi.org/10.1016/0002-9610(91)90364-J)
- [62] Ishigami, K., Zhang, Y., Rayhill, S., Katz, D. and Stolpen, A. (2004) Does Variant Hepatic Artery Anatomy in a Liver Transplant Recipient Increase the Risk of Hepatic Artery Complications after Transplantation? *American Journal of Roentgenology*, **183**, 1577-1584. <https://doi.org/10.2214/ajr.183.6.01831577>
- [63] Christoforidis, E., Vasiliadis, K., Goulimaris, I., Tsalis, K., Kanellos, I., Papachileas, T., Tsorlini, E. and Betsis, D. (2007) A Single Center Experience in Minimally Invasive Treatment of Postcholecystectomy Bile Leak, Complicated with Biloma Formation. *Journal of Surgical Research*, **141**, 171-175. <https://doi.org/10.1016/j.jss.2006.07.012>
- [64] Lee, J.H. and Suh, J.I. (2007) A Case of Infected Biloma Due to Spontaneous Intrahepatic Biliary Rupture. *The Korean Journal of Internal Medicine*, **22**, 220-224. <https://doi.org/10.3904/kjim.2007.22.3.220>

- [65] Lebensburge, J., Esbenshade, A., Blakely, M., Hankins, J. and Wang, W. (2008) Biloma and Pneumobilia in Sickle Cell Disease. Brief Report. *Pediatric Blood Cancer*, **51**, 153-316. <https://doi.org/10.1002/pbc.21575>
- [66] Miro, A.G., De Seta, C., Arenga, G., Russo, M. and Lombardi, D. (2002) Treatment of Major Iatrogenic Lesions of the Bile Ducts. *Annali Italiani di Chirurgia*, **73**, 35-39.
- [67] Mohammad, M.K., Zhou, Z., Cave, M., Barve, A. and McClain, C.J. (2012) Zinc and Liver Disease. *Nutrition in Clinical Practice*, **27**, 8-20. <https://doi.org/10.1177/0884533611433534>
- [68] Jagadeeswaran, R., *et al.* (2018) The Impact of Selenium Deficiency on a Sickle Cell Disease Mouse Model. *Blood*, **132**, 3645. <https://doi.org/10.1182/blood-2018-99-111833>
- [69] Tayo, B.O., Akingbola, T.S., Salako, B.L., *et al.* (2014) Vitamin D Levels Are Low in Adult Patients with Sickle Cell Disease in Jamaica and West Africa. *BMC Hematology*, **14**, Article No. 12. <https://doi.org/10.1186/2052-1839-14-12>
- [70] Saeed, A., Hoekstra, M., Hoeke, M.O., Heegsma, J. and Faber, K.N. (2017) The Interrelationship between Bile Acid and Vitamin A Homeostasis. *BBA Molecular and Cell Biology of Lipids*, **1862**, 496-512. <https://doi.org/10.1016/j.bbalip.2017.01.007>
- [71] Kozeniecki, M., Ludke, R., Kerner, J. and Patterson, B. (2020) Micronutrients in Liver Disease: Roles, Risk Factors for Deficiency, and Recommendations for Supplementation. *Nutrition in Clinical Practice*, **35**, 50-62. <https://doi.org/10.1002/ncp.10451>
- [72] Kamineni, P., Chirla, S., Dinh, K., Hasan, S., Nidhiry, E., Kwagyan, J., Naab, T., Lombardo, F., Castro, O. and Dawkins, F. (2006) Low Cobalamin Levels in African Americans with and without Sickle Cell Disease. *Journal of the National Medical Association*, **98**, 352-356.
- [73] Ajayi, O.I., Bwayo-Weaver, S., Chirla, S., *et al.* (2013) Cobalamin Status in Sickle Cell Disease. *International Journal of Laboratory Hematology*, **35**, 31-37. <https://doi.org/10.1111/j.1751-553X.2012.01457.x>
- [74] Czaja, A.J. (2004) Autoimmune Liver Disease. *Current Opinion in Gastroenterology*, **20**, 231-240. <https://doi.org/10.1097/00001574-200405000-00007>
- [75] Autoimmune Hepatitis|Genetic and Rare Diseases Information Center (GARD)—An NCATS Program. rarediseases.info.nih.gov.
- [76] Jitraruch, S., Fitzpatrick, E., Deheragoda, M., *et al.* (2017) Autoimmune Liver Disease in Children with Sickle Cell Disease. *The Journal of Pediatrics*, **189**, 79-85.e2. <https://doi.org/10.1016/j.jpeds.2017.06.035>
- [77] Maher, M.M. and Mansour, A.H. (2009) Study of Chronic Hepatopathy in Patients with Sickle Cell Disease. *Gastroenterology Research*, **2**, 338-343. <https://doi.org/10.4021/gr2009.12.1327>

Abbreviations

Sickle Cell Disease (SCD), Hemolytic Benign Hyperbilirubinemia (HBH), Sickle Ischemic Hepatic Crises (SIHC), Sickle Sever Ischemic Hepatic Crises (SSIHC), Sickle Hepatic Sequestration (SHS), Sickle Hepatic Infarction (SHI), Sickle Budd-Chiari Syndrome (SBS), Sickle Cholelithiasis (SCh), Sickle Choledocholithiasis (SChd), Hepatitis C Viral (HCV), Hepatitis B Viral (HBV), Coronavirus Disease 2019 (COVID-19), Drug-Induced Liver Injury (DILI), End-Stage Liver Disease (ESLD), Computed Tomography (CT), Magnetic Resonance (MR), Autoimmune Hepatitis (AILD), Lactate Dehydrogenase (LDH), Aspartate Transaminase (AST)