Review

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Liver involvement in hemolytic anemias

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ABSTRACT

Hemolytic anemias in childhood comprise a heterogeneous group of hereditary and acquired diseases that may be associated with liver involvement through multiple mechanisms. Chronic hemolysis leads to a sustained increase in unconjugated bilirubin, with a risk of pigmentary cholelithiasis; ineffective erythropoiesis and repeated transfusions contribute to iron overload and the development of chronic liver disease. In certain conditions, such as sickle cell anemia, vaso-occlusive events can cause acute and chronic liver damage. Furthermore, there are well-documented associations between autoimmune hemolytic anemias and immune-mediated liver diseases.

This review analyzes the main types of hemolytic anemia associated with liver disease in children, including thalassemias, hereditary spherocytosis and elliptocytosis, sickle cell anemia, pyruvate kinase deficiency, and autoimmune hemolytic anemias. The review describes pathophysiological mechanisms, clinical and biochemical manifestations, diagnosis, treatment, and follow-up. Early recognition of liver involvement allows for optimized treatment and the prevention of potentially serious complications.

Keywords: *hemolytic anemia; liver diseases; thalassemia; hereditary spherocytosis; sickle cell anemia.*

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INTRODUCTION

Liver complications associated with hemolytic anemias may result directly from a sustained increase in the supply of unconjugated bilirubin to hepatocytes, from iron accumulation secondary to repeated transfusions, from recurrent vascular obstruction due to the abnormal shape of red blood cells, or from mutations affecting the same enzyme in both the liver and red blood cells. Gallstones result from chronic hemolysis, which leads to the excretion of monoconjugated bilirubin into the bile. Monoconjugated bilirubin is less soluble than biconjugated bilirubin, which promotes the formation of crystals and, subsequently, gallstones.

Autoimmune liver diseases may also be associated with autoimmune hemolytic anemia and require intensive immunosuppressive treatment.

In this review, we summarize the current state of knowledge on this topic, emphasizing the clinical features that enable early diagnosis of liver complications (*Table 1*).

THALASSEMIAS

Thalassemias are a group of inherited disorders of hemoglobin synthesis characterized by reduced or absent production of one or more globin chains, leading to chronic hemolytic anemia of varying severity. In pediatrics, the forms with potential liver involvement are β-thalassemia major and β-thalassemia intermediate. β-thalassemias are caused by mutations in the *HBB* gene, located on chromosome 11, which result in a partial (β+) or complete (β^0) reduction in the synthesis of the beta globin chain. The condition is inherited in an autosomal recessive pattern. The combination of two severe alleles is associated with β-thalassemia major, while less severe combinations result in intermediate or non-transfusion-dependent phenotypes. Symptoms typically begin around 6 months of age, when the physiological conversion from fetal to adult hemoglobin occurs.[1-3]

In their most severe forms, α-thalassemias can cause significant hemolysis; however, their impact on the liver in pediatric patients is generally less severe.[2,4]

The reduction in beta-chain synthesis leads to an imbalance characterized by the accumulation of unstable free alpha chains in erythroid precursors. These chains precipitate in the cytoplasm, induce oxidative stress and cellular apoptosis, and lead to marked ineffective erythropoiesis. Erythrocytes that reach the circulation are more fragile and are destroyed prematurely, contributing to chronic hemolytic anemia.[1,2,5]

Ineffective erythropoiesis and chronic anemia suppress hepatic hepcidin production, which increases intestinal iron absorption. In transfusion-dependent forms, this mechanism compounds iron overload secondary to repeated administration of blood products, resulting in secondary hemochromatosis. Iron is progressively deposited in hepatocytes and Kupffer cells, leading to oxidative stress, chronic inflammation, stellate cell activation, and progressive fibrosis.[6,7]

Hepatic extramedullary erythropoiesis, which is common in intermediate forms, contributes to hepatomegaly and distortion of

Table 1. Disease, mechanisms of liver damage, and liver complications

Disease	Mechanisms	Liver complications
Thalassemia	Multiple transfusions	Hemochromatosis
	Bile precipitation	Cholelithiasis
Spherocytosis	Bile precipitation	Cholelithiasis
Sickle cell anemia	Vaso-occlusive crises	Autoimmune hepatitis
	Tissue necrosis	Sclerosing cholangitis
	Bile precipitation	Cholelithiasis
Pyruvate kinase deficiency	Decreased cellular ATP production	Hepatocyte necrosis
	Bile precipitation	Intra- and extrahepatic cholelithiasis
Hemolytic anemia – giant cell hepatitis	Autoantibodies	Hepatocyte necrosis

Diseases that cause hemolysis and its hepatic complications, which may result from similar mechanisms—as in the case of cholelithiasis—or differ depending on the systemic or local consequences of each of these causes of hemolysis or due to their treatment.

the sinusoidal architecture. In conjunction with iron overload, chronic inflammation may play a role in the development of liver fibrosis and, in selected cases, portal hypertension, even in young patients. Its isolated contribution to the development of cirrhosis is rare.[5-7]

From a clinical standpoint, patients may present with persistent elevations in transaminases—generally mild to moderate—associated with hyperferritinemia. Hepatic iron concentration, best assessed by magnetic resonance imaging, is one of the main indicators of iron overload and the risk of liver damage in patients with thalassemia. Values greater than 7 mg of iron per gram of dry weight are associated with an increased risk of liver fibrosis. In comparison, concentrations greater than 15 mg/g are linked to a high risk of cirrhosis and portal hypertension. Liver elastography can be used as a complementary noninvasive method for the longitudinal assessment of liver stiffness and the monitoring of fibrosis in patients with thalassemia. However, its results should be interpreted with caution, as hepatic iron overload, inflammation, and extramedullary erythropoiesis can increase liver stiffness regardless of the degree of fibrosis. Although serum ferritin is an indirect marker and may be influenced by inflammatory processes or concomitant liver damage, it remains a useful tool for long-term follow-up. Values consistently above 1000 ng/mL are associated with significant iron overload, and levels above 2500 ng/mL have been linked to an increased risk of liver damage. The goal of chelation therapy is to maintain serum ferritin levels between approximately 500 and 1000 ng/mL and a hepatic iron concentration below 7 mg/g, adjusting the treatment strategy according to age, clinical phenotype, and type of thalassemia. Liver biopsy should be reserved for selected situations, such as suspected associated liver disease not attributable exclusively to iron overload.[2,5]

In thalassemia, estimates from clinical series indicate that the prevalence of gallstones is around 10-15%, although specific data from well-defined pediatric cohorts are scarce.[7,8]

HEREDITARY SPHEROCYTOSIS AND HEREDITARY ELLIPTOCYTOSIS

In hereditary spherocytosis, mutations primarily affect the *ANK1* (ankyrin), *SPTB* and *SPTA1* (beta and alpha spectrin), *SLC4A1* (band 3), and *EPB42* (protein 4.2) genes. Inheritance is predominantly autosomal dominant, although autosomal recessive forms exist, generally associated with more severe presentations.[9,10]

In hereditary spherocytosis, defects in the proteins that anchor the cytoskeleton to the lipid bilayer, lead to a progressive loss of membrane surface area, with relative preservation of cell volume. As a result, red blood cells take on a spherical shape, with a lower surface-to-volume ratio and a marked decrease in their deformability. These cells are preferentially trapped and destroyed in the spleen, leading to chronic extravascular hemolysis.

Hereditary elliptocytosis is associated with mutations in *SPTA1, SPTB*, and *EPB41* (protein 4.1); most cases follow an autosomal dominant pattern of inheritance, with variable penetrance and expressivity. Severe forms, such as hereditary pyropoikilocytosis, are usually associated with complex allelic combinations or autosomal recessive inheritance.[9,10]

In hereditary elliptocytosis, abnormalities in horizontal cytoskeletal interactions lead to mechanical instability of the membrane, resulting in the elliptical deformation of red blood cells. In most patients, hemolysis is mild or absent. However, in severe cases, erythrocyte destruction comparable to that seen in spherocytosis may be observed.[9-11]

Liver involvement in both conditions is indirect and secondary to chronic hemolysis. The most common manifestation is pigmentary cholelithiasis, the prevalence of which increases with age and can be observed as early as childhood, even in patients with mild anemia.[11-13]

Hepatomegaly is usually mild and is not associated with primary hepatocellular damage. Liver function tests are usually normal, except for indirect hyperbilirubinemia. Progression to significant chronic liver disease is rare and should prompt an investigation into associated causes.

From a clinical standpoint, in children with hereditary spherocytosis or elliptocytosis, the onset of persistent jaundice, recurrent abdominal pain, or elevated cholestatic enzymes should prompt an ultrasound evaluation of the biliary tree. Some cases may be complicated by cholecystitis, cholangitis, or biliary pancreatitis. Splenectomy, when indicated, reduces hemolysis and the risk of biliary complications, although it does not eliminate the possibility of gallstones.

In series involving ultrasound follow-up, cholelithiasis has been identified in approximately 30-40% of cases, with diagnosis frequently occurring between the ages of 4 and 13 years.

In pediatric patients with hemolytic anemia, cholelithiasis is often asymptomatic and is detected during follow-up ultrasound examinations (*Table 2).* The management of asymptomatic cholelithiasis is watchful, with clinical and imaging follow-up, as there is no evidence to support medical treatment with ursodeoxycholic acid for pigment gallstones. Cholecystectomy is indicated in the presence of recurrent symptoms or complications, following criteria similar to those for the general pediatric population. In hereditary spherocytosis, concomitant cholecystectomy is recommended when gallstones are present at the time of a splenectomy, even in the absence of symptoms. In thalassemia, surgery is reserved for symptomatic or complicated cases.[11-14]

SICKLE CELL ANEMIA – DREPANOCYTIC ANEMIA

Sickle cell anemia results from mutations in the gene that encodes the beta globin chain (*HBB* gene), which lead to hemoglobin S (HBS). In hypoxic conditions, hemoglobin S polymerizes, causing deformation and increased stiffness of the red blood cells. These changes lead to vascular occlusion, vasculopathy, chronic hemolytic anemia, and tissue damage. This group includes patients with homozygous mutations in beta-globin, as well as heterozygotes for HbS/β-thalassemia, HbS/HbC, and other less common variants. In the most severe cases, bone marrow transplantation may be indicated.

Several liver complications have been described in these patients, some of which are associated with significant morbidity and even mortality.[15] The most common is cholelithiasis, which has a prevalence of between 40% and 60% among patients by adolescence or in young adults.[15,16]

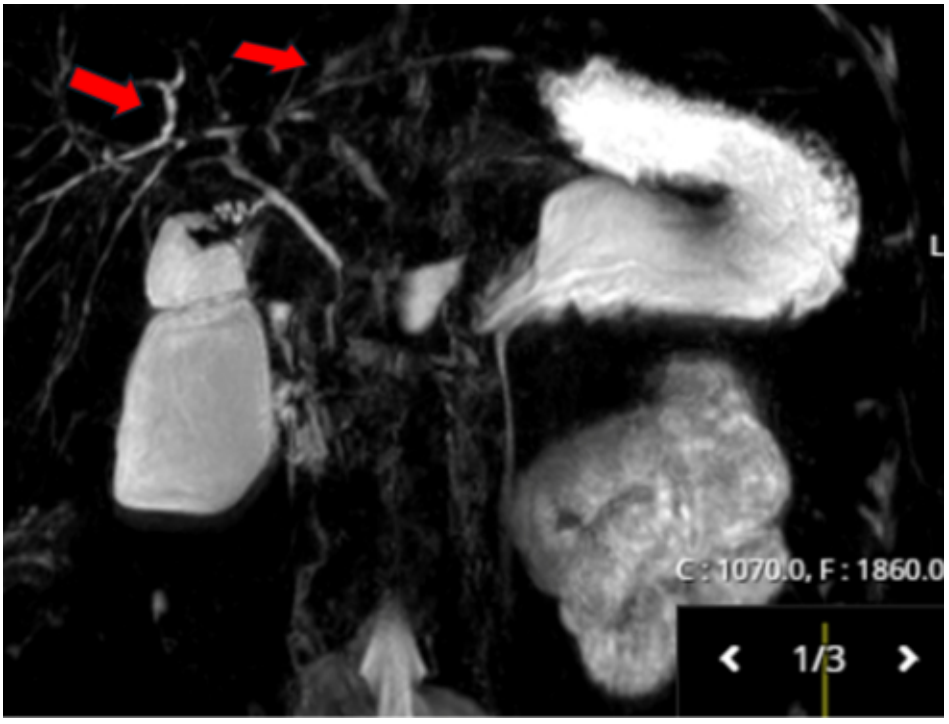
The most serious acute complication, observed in approximately 6% of cases, is hepatic sinusoidal vaso-occlusive disease, which can lead to severe acute liver failure.[17] In these cases, obstruction of intrahepatic circulation causes tissue ischemia, the formation of oxidative radicals, and reperfusion injury. In this context, we must avoid performing a liver biopsy due to the high risk of uncontrollable intraperitoneal hemorrhage. The symptoms of this complication range from moderate, such as liver pain, to severe jaundice and liver failure or even multiple organ failure.[15]

The incidence of autoimmune hepatitis is higher in patients with sickle cell disease than in the general population.[18] These children and adolescents are at increased risk of developing type 1 autoimmune hepatitis, characterized by the presence of antinuclear antibodies (ANA) and, less frequently, anti-smooth muscle antibodies (ASMA). Elevated immunoglobulin G (IgG), a common finding in autoimmune hepatitis, is almost always present in patients with sickle cell disease. However, many have hyper-IgG without histological evidence of autoimmune hepatitis. One possible explanation for this finding is chronic immune stimulation secondary to recurrent tissue destruction due to vascular obstruction. In these patients, increased CD4 lymphocytes, natural killer (NK) cells, and elevated levels of circulating gamma interferon have been shown. Atypical anti-LKM (liver-kidney microsomes) autoantibodies have been detected in patients with sickle cell anemia. The antigens against which these autoantibodies are directed have not been identified. There are several hypotheses to explain the appearance of these anti-LKM antibodies: 1) drug-induced, 2) a consequence of chronic hemolysis, 3) cellular damage secondary to episodes of vaso-occlusion, or 4) secondary to iron accumulation in hepatocytes.[19]

Recurrent vascular obstruction, with consequent ischemia, may be responsible for the progressive destruction of the bile ducts and, in the medium to long term, may lead to cholangiopathy of varying severity in approximately 1% of patients.[20] These patients may progress to cirrhosis and liver failure, preceded by episodes of cholestasis and, occasionally, cholangitis. The need for endoscopic dilations and removal of biliary stones is more common in adults than in children and adolescents. These conditions are considered a form of sclerosing cholangitis secondary to ischemic cholangiopathy (*Figures 1 and 2*).

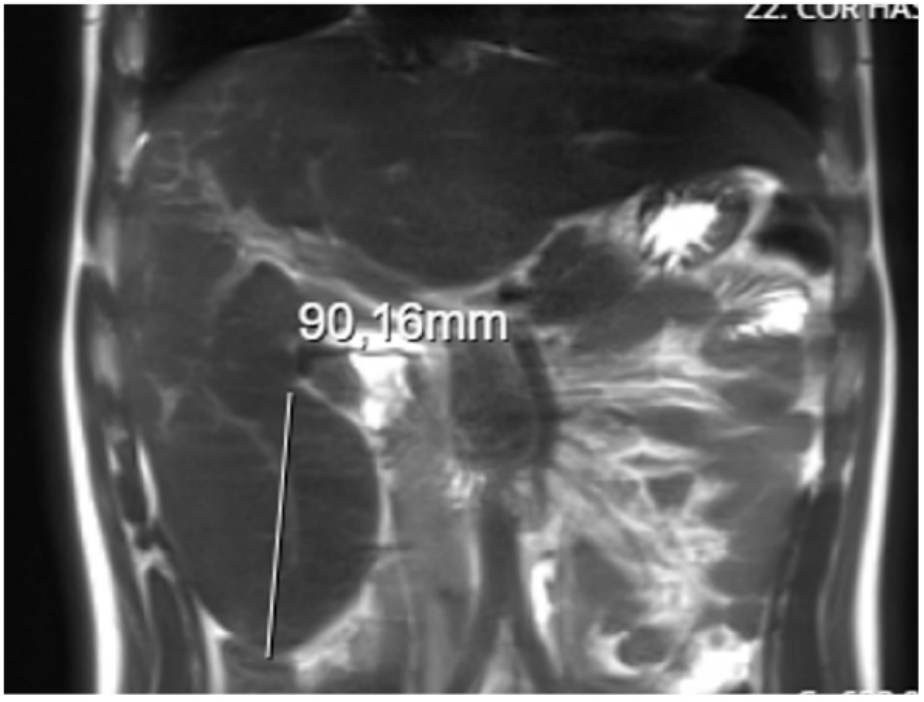
Elevated transaminase levels are common in these children, although they generally do not exceed two or three times the upper limit of normal. Aspartate aminotransferase (AST) levels are usually higher than those of alanine aminotransferase (ALT), because the AST enzyme is also found in red blood cells and increases as a result of hemolysis. Elevated gamma-glutamyl transferase (GGT) levels should prompt an evaluation for biliary tract disease. In cases of persistently elevated transaminases associated with autoantibodies and hyper-IgG, a liver biopsy is recommended before initiating immunosuppressive therapy (*Figures 3 and 4*). It is important to remember that, once the diagnosis

Figure 1. Cholangiopathy in a patient with sickle cell diseas



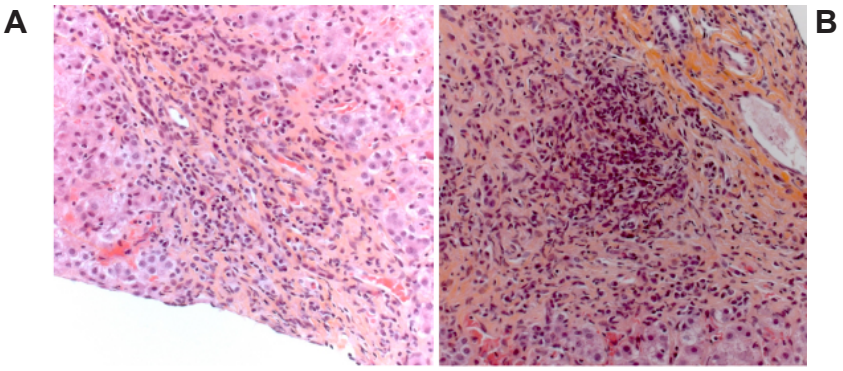
Magnetic resonance cholangiography with stenosis and segmental dilations of the intra- and extrahepatic bile ducts.

Figure 2. Cirrhosis in a patient with sickle cell disease



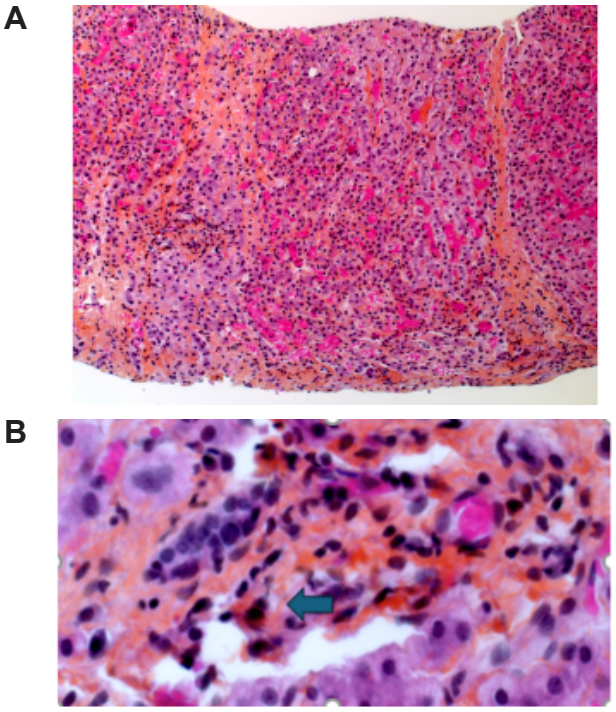
Macroscopic appearance of the liver with nodular architecture and the presence of a dominant nodule measuring approximately 9 cm in the right lobe.

Figure 3. Histological specimens from a patient with sickle cell anemia, elevated serum immunoglobulin G, and circulating antinuclear and anti-smooth muscle autoantibodies



A. Portal fibrosis with lymphoplasmacytic inflammatory infiltrate and interfacial hepatitis.
B. Similar histological features with the additional presence of a lymphocytic cluster in the portal space.

Figure 4. Male patient with sickle cell anemia, history of cholecystectomy and normal serum bilirubin; gamma-glutamyl transferase levels exceed those of alanine aminotransferase/aspartate aminotransferase



A. Cirrhosis and signs of vaso-occlusive disease: dilated sinusoids and the presence of red blood cells within them.
B. Portal space with biliary tract involvement and a lymphocytic inflammatory infiltrate (arrow).

of autoimmune hepatitis is confirmed, treatment must take into account the potential increase in corticosteroid-induced vaso-occlusive crises. If GGT remains persistently elevated, magnetic resonance cholangiopancreatography (MRCP) is mandatory. Patients with sickle cell disease may require a liver transplant during childhood. In these cases, due to the hemolytic disease, postoperative complications can be severe, primarily vaso-occlusive crises.[21]

PYRUVATE KINASE DEFICIENCY

Mutations in the *PKLR* gene cause pyruvate kinase deficiency (L stands for liver and

R stands for red blood cells) and are inherited in an autosomal recessive pattern. However, heterozygous patients may exhibit some degree of hemolysis. This enzyme catalyzes a key step in glycolysis; its deficiency leads to a shortage of adenosine triphosphate (ATP), which is particularly significant in red blood cells, which lack mitochondria and rely on this metabolic pathway for energy production.

In cases of severe anemia requiring frequent transfusions, iron accumulation in the liver can lead to secondary hemochromatosis, necessitating the use of iron chelators. Splenectomy can reduce hemolysis and lower the risk of this complication. Cholelithiasis may develop early, and following a cholecystectomy, the possibility of intrahepatic bile duct stones should be anticipated, with a risk of progression to biliary cirrhosis.[22,23]

In rare cases, certain mutations in the *PKLR* gene are responsible for severe intrauterine hemolysis, leading to fetal hydrops, or may cause severe neonatal cholestasis, characterized by obstruction of the bile canaliculi and normal GGT levels, and, in severe cases, progression to liver failure.[24] In these children, morbidity and mortality are very high, and liver transplantation combined with simultaneous splenectomy is a therapeutic option. Several hypotheses attempt to explain this course: 1) extensive obstruction of the biliary canalicular network, with accumulation of bile products in hepatocytes; 2) decreased ATP production and increased hepatocellular oxidative stress; and 3) a marked increase in hepatic extramedullary erythropoiesis, with local inflammation.

A comparative analysis of patients with different mutations and varying degrees of hemolysis and liver involvement shows that there is no strict genotype-phenotype correlation in patients with pyruvate kinase deficiency; therefore, the prognosis cannot be predicted for an individual patient.

COOMBS-POSITIVE HEMOLYTIC ANEMIA

The most common presentation is observed in the neonatal period, in newborns, due to maternal-fetal blood group incompatibility. The most severe forms, which are now preventable, are those secondary to Rh incompatibility. Cases of ABO incompatibility are generally less severe, although they can present with cholestasis as early as the first day of life. The formation of bilirubin precipitates in the bile canaliculi is responsible for this clinical presentation, descriptively termed “thick bile cholestasis”. The course is usually benign, with resolution within days or weeks.

In children younger than 5 years of age, Coombs-positive autoimmune hemolytic anemia may be associated with giant cell hepatitis. This disease, mediated by autoantibodies directed against erythrocyte membrane antigens and antibodies against the hepatocyte membrane, may present as severe hepatitis with liver failure.[25] The diagnosis is confirmed by liver biopsy, which reveals giant cell transformation of hepatocytes and deposition of the complement membrane attack complex (MAC), as demonstrated by immunohistochemical techniques.[26] Treatment consists of immunosuppression; B-cell depletion through the administration of monoclonal antibodies against the CD20 antigen is particularly effective.[27]

In patients with type 1 autoimmune hepatitis, an association with autoimmune hemolytic anemia has also been reported. In these cases, both hemolysis and hepatitis typically respond favorably to immunosuppressive therapy (*Tables 1 and 2*).

CONCLUSION

Hemolytic anemias are a major cause of liver involvement in childhood, with manifestations ranging from mild biochemical abnormalities to chronic liver disease, portal hypertension, and liver failure. The pathophysiology includes

Table 2. Prevalence of cholelithiasis in pediatric hemolytic anemias

Disease	Approximate prevalence of cholelithiasis	Comments
β-thalassemia	8–15% in children; increases during adolescence	More common in intermediate thalassemia and in splenectomized patients
Hereditary spherocytosis	20-40%	The most common form of chronic pediatric hemolysis
Sickle cell disease	15-45% depending on age	A marked increase after age 10
Pyruvate kinase deficiency	30-45%	Associated with severe chronic hemolysis

chronic hemolysis, ineffective erythropoiesis, iron overload, vascular obstruction, and immunological mechanisms. The spectrum and severity of liver damage vary depending on the underlying condition, the patient's age, and the timing of treatment. In pediatric observational studies of cholelithiasis, more than one-third of children with gallstones had an associated hemolytic disorder.

Systematic follow-up of children with hemolytic anemia should include periodic evaluation of the liver and biliary tract. Early identification of liver involvement and prompt intervention can favorably influence the course of the disease and improve long-term prognosis. ■

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