SPECIAL ISSUE ARTICLE

An Overview of Cirrhosis in Children

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ABSTRACT

Cirrhosis is the end result of nearly all forms of progressive liver disease. The diffuse hepatic process can be characterized as a state of inflammation progressing to fibrosis and resulting in nodular regeneration, ultimately leading to disorganized liver architecture and function. The underlying etiology of cirrhosis in children may often differ from adults owing to specific disease processes that manifest in childhood, including biliary atresia, galactosemia, and neonatal hepatitis. Although basic management strategies in children are similar to those in adults, the care given to children with cirrhosis must keep the child's growth and development of paramount importance. **[*Pediatr Ann*. 2016;45(12):e427-e432.]**

Progressive liver disease in children, which culminates in the development of cirrhosis, remains multifaceted as many childhood hepatic diseases are different from those experienced by adults. Pediatric patients are at a unique state of growth and development. Their nutritional state is easily compromised by their chronic disease, and its repletion is vital for survival. We present an in-depth review of the several manifestations, complications, and management strategies that clinicians should be aware of when caring for children with cirrhosis (**Table 1**).

ILLUSTRATIVE CASE

A 13-year-old previously healthy girl presented to the emergency department for worsening scleral icterus. She reported that her eyes had been "yellow" off and on for the past 2 years and had acutely worsened in the 2 weeks prior to her presentation. The worsening was also accompanied by vague abdominal pain. She denied fever, emesis, or diarrhea and stated that her stools were soft and light in color without blood or mucus. She did endorse a recent history of pruritus throughout her trunk and lower extremities as well as recurrent nosebleeds. She denied any recent medication use or history of allergies. She denied any known family history of liver, gastrointestinal, or autoimmune diseases.

Her physical examination was remarkable for profound scleral icterus and an irregularly firm liver edge palpable 3 cm below the right costal margin with a span of 14 cm. She also had a palpable spleen tip 4 cm below the left costal margin. Initial laboratory values were significant for a normocytic anemia (hemoglobin 8.7 g/dL), thrombocytopenia (59×10^3 U/L), coagulopathy (international normalized ratio 2.1), hypoalbuminemia (2.2 g/dL), elevated protein gap (total protein 8.3 g/dL), and hepatitis/cholestasis (aspartate aminotransferase 304 U/L, alanine aminotransferase 133 U/L, and direct bilirubin 11.8 mg/dL). An abdominal ultrasound showed hepatomegaly with increased echotexture and splenomegaly. She received vitamin K and fresh frozen plasma prior to a transjugular liver biopsy, which showed macronodular cirrhosis with features of autoimmune hepatitis. She was given a course of steroids. She was subsequently listed for liver transplantation after failing to respond to therapy.

PATHOPHYSIOLOGY

The process of cirrhosis is complex and multifactorial but is based on the basic concepts of inflammation, fibrosis, and regeneration. The initial hepatocyte injury causes parenchymal cell destruction and eventual replacement with new hepatocytes. The inflammatory cascade is triggered and associated with the deposition of extracellular matrix. This altered extracellular matrix, including collagen, is the foundation for the formation of fibrosis. Although the exact mechanism leading to fibrosis remains

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TABLE 1.

Etiologies and Diagnostic Tests of Choice for Cirrhosis in Children

Disorder	Diagnostic Test of Choice
Biliary atresia	Intraoperative cholangiogram
Choledochal cyst	Ultrasound, MRCP
Primary sclerosing cholangitis	Ultrasound, MRCP, liver biopsy
HBV	HBeAg/antibody, HBV DNA
HCV	HCV antibody, HCV RNA
Autoimmune hepatitis	ANA, anti–smooth muscle antibody, anti–liver-kidney-microsomal antibody
Alpha1-antitrypsin deficiency	Serum alpha1–antitrypsin level and phenotype
Galactosemia	Urine-reducing substances, RBC galactose-1-phosphate uridyl transferase
Cystic fibrosis	Sweat chloride test, genetic testing
Alagille syndrome	Liver biopsy, physical examination findings, genetic testing
Wilson's disease	Ceruloplasmin, 24-hour urine copper quantification, slit-lamp examination, liver copper concentration, Kayser-Fleischer rings

Abbreviations: ANA, antinuclear antibody; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; MRCP, magnetic resonance cholangiopancreatography; RBC, red blood cell.

unknown, the hepatic stellate cell has gained attention for its role in the excess production of extracellular matrix. The regenerative process ensues to replace damaged cells by stimulating hepatocyte synthesis and promoting proliferation involving the specific cytokines epidermal growth factor, transforming growth factor-alpha/beta, and fibroblast growth factor.[1] The end result is a structurally abnormal liver with altered function.

CLASSIFICATION

Cirrhosis can be described based on morphological appearance (micronodular vs macronodular), histological appearance (periportal vs centrilobular vs biliary vs mixed), or by the clinical status of the patient (compensated vs uncompensated). The latter can help stratify those asymptomatic or stable patients from those who are no longer responding to supportive measures. Children with uncompensated cirrhosis should get the urgent or emergent care required.

CLINICAL FEATURES

General

The end results of progressive liver disease can affect any organ system within the body. Children with cirrhosis may demonstrate a wide array of clinical features, from asymptomatic with poor growth to the classic signs of abdominal distension, ascites, edema, portal hypertension, and encephalopathy. It is the responsibility of the clinician to recognize early signs and symptoms consistent with cirrhosis and to manage accordingly (**Table 2**).

Gastrointestinal

Cirrhosis leading to the development of portal hypertension can give rise to many classic features in the gastrointestinal tract, including abdominal distension, ascites, esophageal varices, and caput medusa (prominent abdominal wall veins). Malabsorption of fat secondary to biliary stasis can lead to steatorrhea and can predispose children to fat-soluble vitamin deficiency (vitamins A, D, E, and K). Pigmented gallstones can also be seen secondary to hemolysis from hypersplenism. Hematemesis in the child with cirrhosis secondary to esophageal or gastric varices is an emergency and may be the first sign of cirrhosis in a previously asymptomatic child.

Hematological

Common hematological manifestations include anemia, thrombocytopenia, and coagulopathy (**Table 3**). Chronic gastrointestinal blood loss or hemolysis secondary to hypersplenism can account for the anemia seen in cirrhosis. Similarly, splenic sequestration can lead to a relative thrombocytopenia with smaller than average platelets that are likely due to decreased production or clearance by the reticuloendothelial system.[2] The coagulopathy of cirrhosis is a result of decreased synthesis of hepatic-derived coagulation factors as well as fat malabsorption, leading to a decrease in vitamin K-dependent factors (II, VII, IX, X). The imbalance of hemostasis is well recognized and may lead to not only an increased bleeding risk, but to thromboembolism as well.

Central Nervous System

Neurological manifestations can present as worsening scholastic performance, subtle alterations in sleep patterns, changes in mood or personality, irritability, or drastic mental status changes. The signs of hepatic encephalopathy are staged from mild to severe and can involve changes in mental status, motor function, muscle tone, and reflexes, with or without the presence

of tremor or asterixis. Asterixis is the most characteristic feature of central nervous system involvement and presents as "flapping" tremors of the hand upon voluntary movement.

Dermatological

Skin manifestations of end-stage liver disease attributed to biliary obstruction include jaundice and pruritus. The inability of the liver to conjugate bilirubin leads to its deposition into the skin and sclera, giving the patient an icteric appearance. Although the exact mechanism of pruritus is poorly understood, it has been suggested that elevated bile salts in these patients are pruritogenic and can act on the peripheral nervous system to increase the perception of itch.[3] The presence of vascular changes, such as flushing, pallor, spider angiomata, and palmar erythema, are also manifestations of cirrhosis, especially in disease progression.[4] Muekhrcke's nails have been associated with cirrhosis and arise as horizontal white bands through the nail bed.[5]

Pulmonary

Hypoxia and cyanosis can arise from the development of arteriovenous shunting in the pulmonary vasculature, and is known as hepato-pulmonary syndrome. This arteriovenous shunting can lead to hypoxia and dyspnea with the need for supplemental oxygen. Longstanding cyanosis can manifest as digital clubbing.

Endocrine

Cirrhosis leads to an inability to metabolize and conjugate hormones, inducing a relative state of hyperinsulinemia and subsequently to diabetes mellitus. Similarly, the failure to metabolize certain adrenal hormones can lead to the overproduction of androstenedione, increasing the conversion of estrone to estradiol and causing gynecomastia (which is more pronounced in young males).[6] The decreased hepatic production of testosterone also leads

TABLE 2.

Physical Examination Findings in Children with Cirrhosis

Examination	Findings
General	Cachexia, dysmorphic features, hepatic fetor
Head/ears/eyes/nose/throat	Scleral icterus, bleeding gingiva
Chest/cardiac/pulmonary	Gynecomastia, heart murmur, cyanosis, increased work of breathing, oxygen desaturation, high jugular venous pressure
Abdomen	Distension, caput-medusa, hepatomegaly, "shrunken-liver," enlarged left hepatic lobe, splenomegaly, ascites
Genitourinary	Inguinal hernias, testicular atrophy, hydrocele, hemorrhoids
Musculoskeletal	Wasting of muscles, decreased subcutaneous fat, bone fractures
Skin/hair	Jaundice, flushing, palmar erythema, pallor, spider nevi, telangiectasias, Muekhrcke's nails, bruising, petechiae, xanthomas, alopecia, baldness
Central nervous system	Decreased mood, mental status changes, increased somnolence, abnormal behavior, night blindness, abnormal deep tendon reflexes, tremors, asterixis, peripheral neuropathy

TABLE 3.

Laboratory, Imaging, and Pathologic Findings in Children with Cirrhosis

Diagnostic Modality	Findings
Complete blood count	Anemia, leukopenia, thrombocytopenia, Burr and target red blood cells
Liver function tests	Mild abnormalities of AST, ALT, low albumin, variable elevation in globulins Elevated conjugated bilirubin in biliary cirrhosis and in decompensated cirrhosis, variable abnormalities in alkaline phosphatase and GGT
Coagulation profile	Prolonged INR unresponsive to vitamin K administration, variable PTT prolongation
Imaging	Hepatic ultrasound or CT scan or MRI: abnormal hepatic texture and nodularity Doppler flow may show hepatofugal portal vein flow or portal vein thrombosis
Pathologic findings	Regenerative nodules and surrounding fibrosis Biliary cirrhosis: hepatocyte and canalicular cholestasis, loss of bile ducts or ductular proliferation

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; GGT, gamma-glutamyl transferase; INR, international normalized ratio; MRI, magnetic resonance imaging; PTT, partial thromboplastin time.

to reduced facial hair and secondary sexual characteristics. Ultimately, many children affected with cirrhosis develop delayed puberty.

MANAGEMENT STRATEGIES BY COMPLICATION

Ascites

Three proposed theories exist explaining the development of ascites: (1) underfilling, (2) overflow, and (3) peripheral arterial vasodilation. The process is initiated by the systemic vasodilation and inappropriate sequestration of fluid in the splanchnic circulation secondary to portal hypertension, which leads to ineffective renal perfusion. The stimulation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system leads to sodium and water retention. With the expansion of the plasma volume, overflow into the peritoneal cavity becomes evident. Hypoalbuminemia and decreased oncotic pressure favor ascitic fluid accumulation.

It has also been suggested that in patients with cirrhosis, excessive hepatic lymph formation may spill directly into the peritoneal cavity via a direct pathway from the liver, bypassing the systemic circulation altogether.[7]

The presence of ascites indicates a stage of worsening liver disease with increased risk of spontaneous bacterial peritonitis, hepato-renal syndrome, and all-cause mortality.[8] Management is geared toward reduction in excess fluid retention while improving oncotic pressure. A low-sodium diet is the first-line therapy to avoid excessive fluid retention. Diuretics are the next course of treatment. Spironolactone, an aldosterone antagonist, tends to be the diuretic of choice due to its potassium-sparing properties. If additional diuresis is required, loop diuretics such as furosemide can also be used, either alone or in combination. Close monitoring of blood pressure and electrolytes should be conducted routinely while a patient is taking diuretics. Some suggest benefit from albumin infusions followed by furosemide when the serum albumin is <3 mg/dL.[9] In severe cases, therapeutic paracentesis can be used for ascites refractory to medical therapies.

Portal Hypertension

The development of portal hypertension results from increased resistance in the portal system secondary to extrahepatic, intrahepatic, or posthepatic causes. Portal hypertension leads to portosystemic collateral formation, which bypasses the liver and can ultimately cause significant complications such as esophageal and gastric varices. Variceal bleeding is a life-threatening emergency. Acute management includes endoscopic evaluation for visualization and therapy, including sclerotherapy (injection of a sclerosing agent directly into the varix) or variceal band ligation (placement of elastic bands onto the varix) to obliterate the vessel. Beta-blocker prophylaxis is recommended for adults with esophageal varices, although its use in children remains unclear.[10]

Difficult-to-manage varices can be relieved by the placement of a surgical or nonsurgical vascular shunt, including a transjugular intrahepatic portosystemic shunt (TIPS), which forms a direct fistula between hepatic veins and the portal system. Although a TIPS can alleviate the increased pressure within the portal circulation, it serves as a palliative measure in the short-term. Complications from TIPS include high-output cardiac failure, hepatic encephalopathy, and shunt stenosis or failure.[11]

Coagulopathy

End-stage liver disease leads to an overall decrease in production of all coagulation factors (both pro- and anticoagulants). The overall imbalance of this tightly regulated cascade leads to coagulopathy. Secondary (indirect) causes, such as thrombocytopenia due to hypersplenism and portal hypertension, can ultimately worsen an already complex scenario that mimics that of disseminated intravascular coagulation. Similarly, the malabsorption of fat-soluble vitamin K, which is an important cofactor for clotting factors II, VII, IX, X in the coagulation cascade, can worsen the coagulopathy.

The treatment of cirrhosis-related coagulopathy depends on the severity of the process, including signs of acute decompensation such as hypotension, acute gastrointestinal blood loss, and shock. In cases suspected to be due to fat malabsorption and vitamin K deficiency, parenteral vitamin K can correct the problem within a few days. In severe cases, treatment consists of supportive care with blood products (packed red blood cells, platelets, fresh frozen plasma) as indicated, vasoconstrictors, and gastric acid suppression. Blood products will transiently correct the acute coagulation derangements, but proper treatment of the underlying process is needed to combat the ongoing coagulopathy.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) refers to a bacterial infection of ascitic fluid not associated with an intestinal perforation or other secondary source of infection.[12] Children with end-stage liver disease have an increased risk for infection, including transient bacteremia, with decreased neutrophilic function and complement defects.[13] These deficiencies predispose children to recurrent and prolonged infections.

Children with SBP can present with ascites in the setting of fever, abdominal

pain or distension, vomiting, irritability, hypotension, or shock. New-onset ascites or unexplained clinical deterioration in a child with end-stage liver disease should prompt an emergent paracentesis to evaluate for SBP. Analysis of ascitic fluid can detect the presence of bacteria, although isolated elevation in white blood cell count within the fluid, without a bacterial source, can also indicate SBP. In most cases, the infection is monomicrobial from enteric pathogens. Cefotaxime is the drug of choice as empiric antibiotic therapy, and a more narrow-spectrum antibiotic can often be used once the culpable organism is isolated. Because the recurrence rate of SBP remains high within the following 12 months, all efforts to minimize risk should be employed, including aggressive diuresis and prophylactic bowel decontamination.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) refers to a potentially reversible neurological process attributed to porto-systemic shunting of toxic metabolites through an altered blood-brain barrier. Ammonia, a potent neurotoxin and byproduct of protein metabolism, has been targeted as the cause of HE, although the absolute value of ammonia in blood has little correlation with degree of encephalopathy. Children may present with a wide spectrum of signs and symptoms consistent with HE. The older child may exhibit more classic features, including alterations in mental status, lethargy, stupor, and coma, whereas an infant may show subtle signs including irritability, excessive sleeping, and poor feeding. Children with cirrhosis should be assessed routinely for any neurological change from baseline.

Treatment strategies are geared toward the decreased production and elimination of ammonia. Protein restriction should not be instituted except in cases of intractable encephalopathy, and even in those cases protein restriction to less than 2 g/kg per day should be avoided, as this will lead to endogenous muscle protein consumption.[14]

Oral antibiotics, such as neomycin or rifaximin, are used to suppress the endogenous production of ammonia-forming bacteria.[15] Lactulose, a semisynthetic disaccharide, is also used frequently. When lactulose reaches the colon, bacteria metabolize it to byproducts, essentially acidifying the feces and trapping ammonia from being absorbed.[16] Combination therapy has also been used in children with some success. Intractable encephalopathy is an indication for liver transplantation.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is characterized as renal insufficiency of unknown origin in a patient with end-stage liver disease. The exact mechanism is poorly understood but is hypothesized to result from blood redistribution and vasoconstriction of renal blood flow in the renal corticomedullary region.[17] There is emerging evidence that non-vasomotor mechanisms play a role as well, including those related to bile cast nephropathy in patients with jaundice due to the direct toxic effect of bilirubin and bile acids on renal tubules. Other factors include the generation of proinflammatory cytokines as a consequence of systemic inflammatory response syndrome or infections.[18]

Management strategies are preventive in nature and involve avoiding nephrotoxic agents and other conditions that may precipitate the development of HRS, such as dehydration, gastrointestinal bleeding, urinary tract obstruction, and sepsis. With proper prevention strategies, the changes seen in HRS can be reversed, but in severe cases hemodialysis is required to maintain electrolyte balance and control azotemia. If medical management does not improve the renal or hepatic failure, then liver transplantation may be the only treatment to reverse renal damage.

NUTRITIONAL CONSIDERATIONS

A principal component in the management of children with end-stage liver disease is centered on sustained growth and development. The etiology of malnourishment in cirrhosis is multifactorial and relies on a combination of metabolic imbalance interfering with protein production, glucose homeostasis, and fat absorption. Growth failure is a key component of the Pediatric End-Stage Liver Disease score. A common indication for listing children for liver transplantation are the morbidities associated with an underlying malnutrition.[19]

A comprehensive nutritional assessment should be completed in any child presenting with end-stage liver disease. Dietary history (formula type and frequency), vitamin and mineral supplementation, and anthropometric measures should be conducted at each visit. Inadequate caloric intake tends to occur more frequently than not, likely secondary to a patient's low-protein, low-sodium diet that may prove to be unpalatable. Similarly, the gastric capacity may be limited due to massive organomegaly or ascites, leading to anorexia. When assessing the nutritional status in these children, close attention should be focused on lean body mass as opposed to weight and body mass index, which can be affected by ascites, edema, and total body water. Simple, noninvasive measures of lean body mass include mid-upper arm circumference and triceps skin fold measurements. Protein intake should not be restricted in these children so long as intractable HE is not

present to allow for normal growth potential.

The most commonly recognized nutritional deficit in children with end-stage liver disease is fat malabsorption. The inability of bile (fat emulsifier) to flow into the small intestine prohibits the proper absorption of this vital macronutrient and can subsequently lead to fat-soluble vitamin deficiency. Children may present with symptoms consistent with a vitamin deficiency, such as dark blindness (vitamin A), inadequate bone mineralization and rickets (vitamin D), peripheral neuropathy (vitamin E), or coagulopathy (vitamin K). Medium chain triglycerides (MCT) are the preferred lipid in cholestasis as they are more easily absorbed by the intestinal epithelium, without the need for bile salt digestion. Although most fat should be in the form of MCT, the complete avoidance of long chain triglycerides is not recommended so as to avoid essential fatty acid deficiency. Proper recognition and supplementation with fat-soluble vitamins and MCT is crucial to the management of nutritional deficiencies of cirrhosis.[20]

Management strategies to prevent nutritional failure in children with cirrhosis are crucial. Children may require an elevated energy intake up to 150% of their estimated daily requirement to counteract their metabolic imbalance.[21] In children with persistent growth failure, supplemental nasogastric tube feedings, using formulas high in MCT oil may be implemented to improve caloric intake. In extreme cases, liver transplantation may be the last resort to correct malnutrition and suboptimal growth.

CONCLUSION

End-stage liver disease in children is complex and multifactorial. The signs and symptoms can range from subtle and asymptomatic to severe with characteristic stigmata of cirrhosis, including ascites, portal hypertension, and encephalopathy. Management should focus on treatment of the underlying disease while allowing the child to achieve and maintain adequate growth and developmental potential. The care of children with end-stage liver disease is multidisciplinary and requires astute recognition and prompt management strategies to combat the complications of the progressive process.

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