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Liver Disease in the Adolescent

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KEYWORDS

• Adolescent • Liver disease • Nonalcoholic fatty liver disease • Hepatitis

KEY POINTS

- There are challenges that must be addressed to effectively care for, not only liver disease in the adolescent but also the patient as a whole.
- Evaluation of an adolescent with new-onset liver enzyme abnormalities should be individualized based on the patient's history and physical exam, but there are a few diseases that need to be ruled out for any adolescent with elevated liver enzymes.
- Due to the development changes occurring in adolescence, monitoring for adherence, risk-taking behaviors, and signs of psychological diseases, such as anxiety and depression, is imperative when caring for an adolescent with liver disease.
- Transition of care to adult-centered care is a continuous process throughout adolescence and should incorporate interventions to promote self-management skills and adherence.

CARING FOR ADOLESCENTS WITH LIVER DISEASE

Adolescence is a unique and sometimes challenging time in a young person's life. This time marks the transition from childhood into adulthood and is exemplified by cognitive, psychosocial, and emotional development, as well as physical and pubertal growth. Furthermore, adolescents are trying to gain independence and create a secure identity during this critical time.[1] However, unparalleled growth of physical, cognitive, and psychosocial development may limit the adolescent's ability to perceive or judge risk appropriately. **Fig. 1** depicts the interdependence between the developmental achievements in adolescence.

Cognitive development during adolescence not only includes the development of more advanced reasoning skills and the ability to think abstractly but also the capacity to think about how others perceive them. As a result of this formal operational thought

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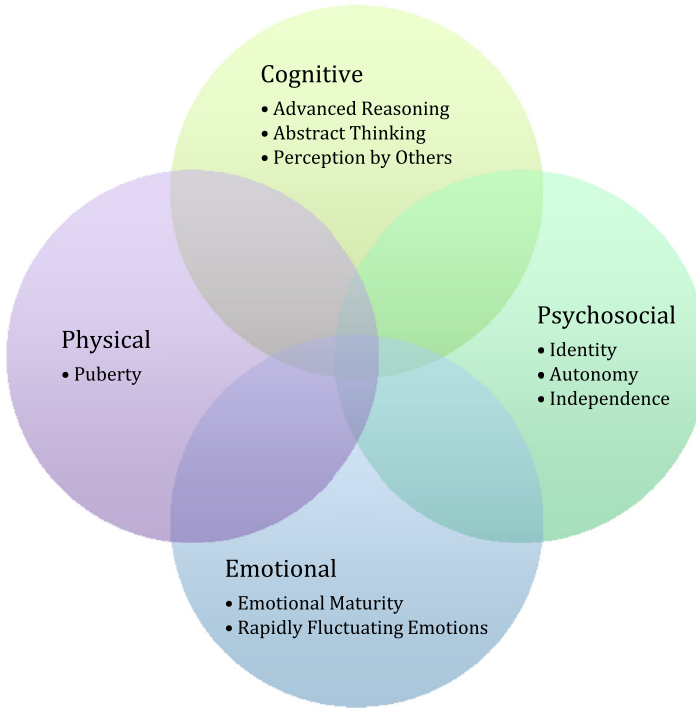

Fig. 1. Adolescent developmental achievements.

process combined with rapid emotional and physical changes during puberty, many youth start to think that everyone is thinking about them, so as to develop an imaginary audience. This thinking can be harmful to an adolescent with a chronic illness or new-onset illness, especially liver disease. A young person may try to deny or hide their illness because they fear the imaginary audience (peers) may find out about their illness, or the adolescent may try to prove the condition does not exist.[2] Because the audience is very real to the adolescent, the clinician must be sympathetic and find solutions to not only address the health care needs of the patient, but also the social needs.

The psychosocial development that occurs during adolescence includes establishing an identity and developing autonomy. As an adolescent explores their identity they may experiment with a variety of behaviors, activities, and peer groups, including risk-taking and dangerous behaviors.[3] For a patient with liver disease, some of these risk-taking behaviors may involve an increased risk because of the underlying disease. It is also during this period that patients may start presenting signs and symptoms of psychological diseases, such as anxiety and depression. Adolescents put such an emphasis on relating to and fitting in a peer group, that having a chronic liver disease and being different may cause symptoms of anxiety or depression. Therefore, it is essential for every adolescent with liver disease to have an established medical home that not only provides anticipatory guidance and health advice to the parents and patient, but also interventions as needed and an open dialogue with the adolescent.[4]

The development of independence is a gradual process for a young person and a time when the peer group influence grows stronger and they are less interested in

parental advice. However, the development of self-management for adolescents with chronic health needs usually lags behind their psychosocial development. One study looking at independent health care behaviors in adolescents with inflammatory bowel disease, reported that many patients 18 years and older were still assisted by parents.[5] There are similar studies in the pediatric liver transplant population reporting that patients diagnosed and/or transplanted at a younger age have increased difficulty in obtaining independence regarding self-management care.[1,6,7] It is imperative for the clinician to foster and encourage the young person's motivation to develop self-management skills throughout adolescence.

Caring for adolescents with liver disease is a gratifying experience. However, these are just a few of the challenges that must be addressed to effectively care for not only the disease but also the patient as a whole.

EVALUATION OF THE ADOLESCENT WITH NEW-ONSET LIVER ENZYME ELEVATION

Up to 9% of asymptomatic people can have elevated liver enzymes including aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), γ-glutamyltransferase (GGT), and/or alkaline phosphatase.[8] An extensive evaluation of all abnormal test results would expose many patients to unnecessary risks and expense; however, failure to evaluate even minor liver enzyme elevations that persist beyond 8 to 12 weeks may mean missing the early diagnosis of a potentially treatable disease. By understanding the pattern of biochemical markers of liver injury, one can further categorize the differential diagnoses for an adolescent patient with new-onset liver laboratory abnormalities.

Elevated ALT and AST suggests liver cell injury and does not evaluate the function of the liver. ALT mainly exists in the liver but can be found in very low concentrations in other tissues. However, AST is found in multiple tissues including liver, cardiac, skeletal muscle, kidney, brain, pancreas, lung, leukocyte, and erthrocyte.[9] Because AST is found in several other tissues, ALT is considered the more liver-specific enzyme. In addition, it has been suggested that ALT correlates with the degree of abdominal adiposity.[10]

Aminotransferase activity may be elevated because of a variety of reasons. **Box 1** reviews potential causes for abnormal aminotransferase activity. Nonalcoholic fatty liver disease (NAFLD) is currently one of the most common causes of aminotransferase elevation in adolescents and adults. Infectious causes of elevated ALT and AST levels must be excluded, including viral hepatitis (A, B, C, E); other viral infections (cytomegalovirus [CMV], Epstein-Barr virus [EBV], herpes simplex virus, varicella zoster virus); and bacteria, fungal, and parasitic infections. Metabolic causes of elevated aminotransferases in the adolescent are Wilson disease, α_1-antitrypsin (A1AT) deficiency, hemochromatosis, and cystic fibrosis (CF). Immunologic causes include autoimmune hepatitis (AIH), acute fatty liver of pregnancy, and HELLP syndrome. Medication- and toxin-induced liver injury is not uncommon in adolescence and can usually be elicited in the history and confirmed by demonstration of a pattern of injury characteristic for the suspected agent on liver biopsy. Other causes of elevated aminotransferase activity include vascular disease, such as Budd-Chiari syndrome, ischemic hepatitis, sinusoidal obstruction syndrome, and infiltrative liver diseases, such as sarcoidosis and amyloidosis. Nonhepatic causes of abnormal aminotransferase levels include cardiac disease, thyroid disease, celiac disease, anorexia nervosa, adrenal insufficiency, myopathy, and strenuous exercise. The clinician should not overlook the possibility of alcoholic liver disease when evaluating the adolescent with elevated liver enzymes, because drinking alcohol is a risk-taking activity that

Box 1
Causes of elevated aminotransferases

- Nonalcoholic fatty liver disease
- Infectious
  - Viral hepatitis (A, B, C, D, E)
  - Epstein-Barr virus
  - Cytomegalovirus
  - Herpes simplex virus
  - Bacterial
  - Fungal
  - Parasitic
  - Severe acute respiratory syndrome
- Metabolic
  - α_1-Antitrypsin deficiency
  - Wilson disease
  - Hemochromatosis
  - Cystic fibrosis
- Immunologic
  - Autoimmune hepatitis
  - Acute fatty liver of pregnancy
  - HELLP syndrome
- Toxin/medication
  - Alcohol
  - Allergic reaction
  - Hepatotoxic medication
- Biliary tract
  - Primary sclerosing cholangitis
  - Alagille syndrome
  - Progressive familial intrahepatic cholestasis
  - Biliary atresia
  - Primary biliary cirrhosis
- Vascular
  - Ischemic hepatitis
  - Sinusoidal obstruction syndrome
  - Budd-Chiari syndrome
- Infiltrative
  - Sarcoidosis
  - Amyloidosis
- Nonhepatic
  - Cardiac disease
  - Celiac disease
  - Thyroid disease
  - Myopathy
  - Malnutrition
  - Anorexia nervosa
  - Adrenal insufficiency
  - Strenuous exercise
  - Macro AST

many young adults partake in with peers or in isolation but do not eagerly discuss with an adult.

Alkaline phosphatase predominately originates from bone and liver, but is also present in the small intestine, kidneys, and placenta. An elevation may suggest biliary obstruction, bile duct epithelium injury, or cholestasis. However, an isolated alkaline phosphatase elevation without a GGT elevation may be caused by bone disease or a time of increased bone growth, as in children and adolescents. Alkaline phosphatase can be fractionated to determine if it is originating from bone or liver. An elevated alkaline phosphatase is usually from the liver if there is simultaneous elevation of other measures of cholestasis. Biliary causes of alkaline phosphatase elevation include cholelithiasis, drug hepatotoxicity, primary sclerosing cholangitis (PSC), and primary biliary cirrhosis. In addition, there are rare cases of benign familial intestinal alkaline phosphatase elevation.

GGT is present in hepatocytes and biliary epithelial cells, and kidney, pancreas, spleen, heart, brain, and seminal vesicles. GGT is the most sensitive marker for biliary

tract disease but is not very specific. It is elevated up to six or seven times the upper limit of normal for the adult reference range in normal, full-term neonates but usually decreases to a normal reference range level by about 6 months of age. Alcohol and drugs, including phenytoin and phenobarbital, may cause GGT elevation.

Prothrombin time/international normalized ratio, glucose, and serum albumin are tests used to evaluate the synthetic function of the liver. These laboratory tests should be evaluated for any patient with new-onset liver enzyme elevations.

The first step in evaluation of a patient with new-onset liver enzyme elevations is a detailed and comprehensive history to identify potential risk factors for liver disease and a thorough physical examination to look for signs of chronic liver disease. The work-up for elevated liver enzymes in an adolescent should be individualized based on the patient's history and physical examination. However, there are a few diseases that need to be ruled out for any adolescent with elevated liver enzymes (**Table 1**). Depending on the acuity of the illness and enzyme elevations, infectious causes must be evaluated. EBV and hepatitis A usually cause a symptomatic, acute self-limited hepatitis. However, hepatitis B and hepatitis C may be diagnosed in an asymptomatic patient, and should always be assessed. Autoimmune hepatitis, A1AT deficiency, and Wilson disease are a few diseases that need to be ruled in or out in all adolescents with elevated liver enzymes despite symptoms. NAFLD may be suspected based on the patient's growth chart and examination. The clinician should ask about any recent illnesses or exposure to people with an illness. Many viruses can cause an acute hepatitis that is self-limited and resolves without sequela. If drug-induced liver injury is high on the differential based on the patient's

Table 1
Evaluation of an adolescent with elevated liver enzymes

Disease	Testing
Hepatitis A	Hepatitis A antibody
Hepatitis B	Hepatitis B surface antibody Hepatitis B surface antigen Hepatitis B core antibody
Hepatitis C	Hepatitis C antibody
Hepatitis E	Hepatitis BE antibody Hepatitis BE surface antigen
EBV	EBV IgM antibody EBV polymerase chain reaction
CMV	CMV IgM antibody CMV polymerase chain reaction
Autoimmune hepatitis	Autoantibodies to nuclei Smooth muscle antibody Liver/kidney microsome antibody Total IgG
α_1-Antitrypsin deficiency	α_1-Antitrypsin phenotype
Wilson disease	Ceruloplasmin serum 24-h urinary copper
Hemochromatosis	Complete blood count Total iron Total iron-binding capacity Transferrin saturation Ferritin

history, the drug in question should be discontinued immediately. Patients that have elevated GGT, alkaline phosphatase, or bilirubin should also have a liver ultrasound to evaluate for any anatomic abnormalities, such as bile duct dilatation, gallstones, or a liver mass.

COMMON LIVER DISEASES IN THE ADOLESCENT

Nonalcoholic Fatty Liver Disease

The prevalence of NAFLD varies widely depending on the population; however, worldwide prevalence of NAFLD is estimated between 6% and 30% with a median of 20% in the general adult population.[11] It is estimated to be about 30% in the United States.[12] Obesity is a common and well-documented risk factor for NAFLD. With the rise in obesity rates in the United States, there is also an increase in the diagnosis of NAFLD, which can lead to nonalcoholic steatohepatitis and cirrhosis. Age, gender, and ethnicity are all associated with the varying prevalence of NAFLD. Fatty liver disease increases with age, and the possibility of disease progression to advance fibrosis increases in older patients. Many studies report male gender as a risk factor for NAFLD.[11] Hispanic individuals also have a significantly higher prevalence of fatty liver disease compared with non-Hispanic whites. Non-Hispanic blacks have a much lower prevalence of NAFLD.[12,13] There is a higher prevalence in patients with metabolic syndrome, type 2 diabetes mellitus, and dyslipidemia.

Patients with NAFLD are usually asymptomatic, but they may have right upper quadrant pain, hepatomegaly, or several nonspecific symptoms including weakness, fatigue, or abdominal discomfort. Mild elevation of aminotransferase activity or hepatomegaly may be the only finding in patients with NAFLD. NAFLD may be suspected based on history and physical examination, but the diagnostic gold standard is still a liver biopsy. Several noninvasive methods for diagnosing NAFLD are being evaluated and may be clinically useful in the future. The only treatment of NAFLD at this time is lifestyle modification with weight loss and increased physical activity, which helps to reduce hepatic steatosis but does not reverse fibrotic changes. Loss of at least 3% to 5% of total body weight is needed to improve steatosis, but weight loss up to 10% may be required to improve necroinflammation.[14,15] A practical approach to a patient suspected of having fatty liver disease based on history and elevated aminotransferases for at least 1 month is to draw laboratory studies to rule out other diseases, such as AIH, A1AT deficiency, Wilson disease, hemochromatosis, and thyroid disease. It is also important to obtain laboratory studies to evaluate for metabolic syndrome because of the high prevalence of metabolic syndrome in patients with NAFLD. If the laboratory results do not point to a specific disease, it is reasonable to defer the liver biopsy for 6 to 12 months to allow the patient time to lose weight and possibly show improvement in the aminotransferases.[16]

Autoimmune Hepatitis

AIH is a chronic hepatitis caused by nonresolving inflammation of the liver of unknown cause. It is characterized by immunologic features and circulating autoantibodies. The onset is usually insidious with many nonspecific symptoms including fatigue, nausea, abdominal pain, joint pain, and jaundice. However, the clinical spectrum is broad and ranges from an asymptomatic presentation to presenting in acute liver failure. AIH is usually suspected and typed based on circulating autoantibodies to nuclei and/or smooth muscle or to liver/kidney microsomes and/or liver cytosol antigen. Patients with AIH may also have high serum globulin concentrations

including a high IgG, elevated aminotransferases, GGT, alkaline phosphatase, and/or bilirubin. Women are affected more frequently (gender ratio, 3.6:1), but it is seen at all ages and in all ethnic groups.[17] Children with AIH may have autoimmune PSC even without inflammatory bowel disease, so it is important to evaluate for PSC in all children with AIH. GGT may be a better indicator of biliary disease in adolescents and children because alkaline phosphatase can be elevated due to bone activity in growing children. Liver biopsy is recommended to establish the diagnosis of AIH and help guide treatment. Interface hepatitis is the most common histologic sign of AIH, but there may also be plasma cell infiltration, lobular inflammation, fibrosis, and rarely granulomas.[18]

Treatment is similar in children and adults. However, all children diagnosed with AIH should be started on treatment at the time of diagnosis regardless of the severity of disease activity because children seem to present with a more severe disease process.[17] Standard therapy for AIH in adolescents usually consists of prednisone with or without azathioprine. The prednisone is typically tapered to a low maintenance dose during the first few months of treatment provided there is prompt response in liver enzymes. There are many side effects related to the use of prednisone, including weight gain, higher body mass index, stunted linear growth, and pubertal delay, which are important to consider when treating adolescents with AIH. Budesonide, a topical steroid, with azathioprine is a reasonable alternative treatment with fewer side effects, including less weight gain and lower body mass index, which may be used to maintain remission in adolescents with steroid-related side effects. Azathioprine is also used as maintenance therapy alone.[19] Some patients are able to completely stop therapy with close serologic monitoring and after 2 to 3 years of biochemical remission and histologic resolution.[20] About 20% of children with type 1 AIH are able to permanently discontinue immunosuppressive therapy without disease recurrence, but this rarely is the case in children with type 2 AIH.[21] Disease refractory to standard therapy typically progresses to cirrhosis and may necessitate liver transplant.

Viral Hepatitis

There are numerous infections, bacterial and viral, that can cause an acute hepatitis that resolves with the infection and does not cause long-term damage. Viral hepatitis including hepatitis A, B, C, and E viruses may cause elevated aminotransferases. Hepatitis A and E cause an acute, self-limited infection and are spread via fecal-oral route. Hepatitis A vaccination is recommended for individuals at risk or traveling. There is currently no vaccination against hepatitis E. Conversely, hepatitis B and C usually present in adolescence as a chronic infection. Aminotransferase activity is typically elevated with acute viral hepatitis, but may be closer to normal in chronic hepatitis, especially hepatitis C. Hepatitis B virus (HBV) may be vertically transmitted from mother to baby or through contact with the blood or other body fluids of an infected person. HBV may cause symptomatic acute hepatitis within the first 6 months of infection, but many individuals are completely asymptomatic and clear the virus within 6 months of contracting. Up to 50% of children who contract the virus before 6 years of age develop chronic hepatitis, and the risk of chronic infection in patients with vertically acquired hepatitis B approaches 90%.[22]

There is no treatment available for acute hepatitis B, but there are treatment regimens for chronic HBV. Vaccination against hepatitis B is the mainstay of hepatitis B prevention. Hepatitis D can cause an acute or chronic infection, but can only replicate in patients with HBV infection. Hepatitis C virus (HCV) is a bloodborne virus that can cause an acute or chronic infection and may also be vertically transmitted. Up to

85% of patients infected with hepatitis C develop chronic HCV. There is not a hepatitis C vaccine, but there are multiple treatments available. Most adolescent patients with HBV and HCV acquired the virus via vertical transmission. However, because of the high-risk behaviors that young adults participate in, it is important to test for HBV and HCV when evaluating an adolescent with elevated liver enzymes even if they have tested negative in the past.

Systemic viral infections can also cause abnormal aminotransferase levels. Elevated ALT and AST caused by EBV is frequently seen in conjunction with acute mononucleosis and a positive monospot test and is usually self-limited. However, EBV serology may need to be evaluated if the monospot test is negative because it does not have a high sensitivity and may be negative early in the course of EBV infection. Jaundice occurs in less than 10% of children with EBV infection.[23] CMV infection in the immune-competent patient generally presents as a subclinical case and is self-resolving. Disseminated CMV infection in the immune-compromised patient may cause severe organ damage or mortality. Herpes simplex virus is predominantly diagnosed in neonatal, pregnant, and immune-compromised patients and presents with fulminant hepatitis and high mortality.

Metabolic Disease

Wilson disease

Wilson disease is an inherited autosomal-recessive metabolic disease that leads to the impairment of cellular copper transport. ATP7B, the defective gene, encodes a hepatic copper-transporting protein that plays a key role in human copper metabolism. This defect results in decreased copper transport from the liver into bile causing excess copper accumulation in several organs but most notably in the liver, brain, cornea, and kidney. The excess hepatic copper leads to hepatocyte damage. The worldwide prevalence of Wilson disease is approximately 1 in 30,000 live births with a slight male predominance.[24,25] Most patients with Wilson disease are diagnosed between the ages of 5 and 35 years and may present with hepatic, neurologic, and/or psychiatric symptoms. Children usually present with liver disease between the ages of 9 and 13 years.[26] The hepatic manifestations of Wilson disease vary greatly and consist of asymptomatic laboratory abnormalities and steatosis, acute hepatitis and acute liver failure with an associated Coombs-negative hemolytic anemia, chronic hepatitis, and cirrhosis. Biochemical abnormalities may include elevated aminotransferases, low serum ceruloplasmin, elevated 24-hour urinary copper, Coombs-negative hemolytic anemia, thrombocytopenia, or coagulopathy. Additional signs and symptoms associated with hepatic Wilson disease are Kayser-Fleischer rings (50% patients with hepatic disease and diagnosed on slit-lamp examination), abdominal pain, hepatomegaly, jaundice, splenomegaly, ascites, upper gastrointestinal bleeding, or mental status changes caused by hepatic encephalopathy.[24] Liver biopsy shows a high hepatic copper concentration.

Treatment of Wilson disease is life long and involves removing the tissue copper that has accumulated and preventing reaccumulation of excess copper. Potent copper chelators (trientene and D-penicillamine) at moderate doses are used to treat copper overload, whereas low doses are used to help prevent copper accumulation. Patients are also maintained on a low-copper diet and avoid copper-rich foods (chocolate, shellfish, nuts, mushrooms, unprocessed wheat). Dietary copper intake in a general diet is about 1 to 5 mg per day and the recommended daily copper intake is 0.9 mg per day for a healthy individual. Patients who present with acute liver failure may require a liver transplant. First-degree relatives of any patient newly diagnosed with Wilson disease need to be screened for Wilson disease.

α_1-antitrypsin deficiency

A1AT deficiency is an underrecognized disorder affecting the lung, liver, and rarely skin. It is the most common known genetic cause of liver disease leading to pediatric liver transplantation. A1AT is a serum glycoprotein synthesized mainly in the liver in large quantities and secreted into the serum. Its physiologic function is to inhibit neutrophil proteases released during periods of inflammation to protect host tissue from nonspecific injury. There are many known mutations of the A1AT gene but most patients with liver disease are homozygous for the Z mutant allele (Pi*ZZ). This occurs approximately 1 in 2000 to 5000 births in North American and European populations.[27] The A1AT mutant Z gene directs the synthesis of a mutant protein that is abnormally folded and retained intracellularly within the hepatocyte rather than being excreted. The accumulation of the mutant protein within hepatocytes triggers a cascade of chronic hepatocellular apoptosis, regeneration, and end-organ injury, which leads to liver injury, cirrhosis, and hepatocelllular carcinoma given the right environmental triggers.[28,29] Patients may present with neonatal hepatitis and cholestasis or as an adolescent with elevated aminotransferases, elevated GGT, and hepatomegaly. Mild liver disease at diagnosis can continue to progress to advanced liver disease. There is currently no medical treatment of A1AT, but liver transplant may be used to treat patients with end-stage liver disease.

Biliary Atresia

Biliary atresia (BA) is an idiopathic, progressive obliterative disease of the extrahepatic biliary tree that presents in neonates with biliary obstruction. It is the most common indication for liver transplant in children. The overall incidence is 1 in 8000 to 19,000 live births and there are 250 to 400 new cases per year in the United States. Once diagnosed with BA a Kasai procedure is promptly performed to enhance the flow of bile. Less than half of patients with BA make it into adolescence with their native liver. The outcomes for adults with BA with their native liver at 20 years are promising with all of them having normal pubertal development and greater than 75% achieving a normal average height. In addition, 60% participate in standard daily activities including 33% holding down employment, 27% being enrolled in school, and 32% being married. Even with all the positive outcomes, 10% report depression and about 5% are heavy drinkers.[30] The hepatic complications associated with BA post-Kasai include portal hypertension (PTN), cirrhosis, gastrointestinal bleeding, late bacterial cholangitis, coagulopathy, and pruritis. PTN and recurrent cholangitis are frequent complications with high morbidity and mortality that necessitate the need for liver transplant. PTN may occur in up to two-thirds of long-term survivor patients with BA and their native liver. It is often defined by complications of PTN, such as gastrointestinal bleed or by endoscopic findings (varices). Some noninvasive markers of PTN include splenomegaly, thrombocytopenia, and low albumin.

There are a few endoscopic therapies available for patients with variceal bleeding including banding and sclerotherapy. Octreotide is usually effective for immediate medical management but is not a long-term therapy. Patients with low bilirubin and variceal hemorrhage have a better prognosis than patients with higher bilirubin levels and variceal bleed.[31] In select patients with compensated liver disease and variceal bleeding refractory to medical and endoscopic therapies, a transjugular intrahepatic portosystemic shunt maybe a viable alternative as a bridge to liver transplant.[32] Cholangitis is another common complication defined as fever, acholic stools, and elevated liver enzymes. It is not uncommon for a patient with suspected cholangitis to have a negative blood culture. Most cholangitis is caused by enteric pathogens including *Escherichia coli*, *Enterobacter*, and *Klebsiella* and treated

effectively with cephalosporins, aminoglycosides, or levofloxacin. However, recurrent cholangitis increases the risk of variceal hemorrhage and thus the need for evaluation for liver transplant. Most adolescent patients with BA and their native liver eventually need a liver transplant.

Cystic Fibrosis

CF is a common disease with an incidence of 1 in 3000 live births and a current life expectancy of 40 years. Less than one-third of patients with CF have clinically significant liver disease. There is a male predominance in patients with CF and liver disease. About 50% of patients with CF and liver disease are noted to have steatosis, whereas up to 12% have cholithiasis, and roughly 5% to 7% have focal to multilobular biliary cirrhosis.[33] CF liver disease is primarily diagnosed in patients with severe CF transmembrane regulator mutations. Absence of CF transmembrane regulator function causes dehydration, concentration, and decreased alkalinization of duct contents producing precipitation of biliary secretions, which leads to biliary obstruction and inflammation causing biliary cirrhosis. Liver enzymes are not a good indicator of hepatic injury because up to 50% of patients with CF liver disease only have intermittently abnormal laboratory studies including elevated aminotransferases and GGT.[34] Elevated bilirubin is uncommon. There are minimal treatment options for CF liver disease. Ursodeoxycholic acid may improve bile flow and liver enzymes and it is postulated that it may have a cytoprotective effect. Some patients have progression of their biliary cirrhosis to multilobular cirrhosis with PTN, but few overall develop ascites and varices. Transjugular intrahepatic portosystemic shunt and banding are effective therapies for PTN secondary to CF liver disease. β-Blockers may cause bronchospasm so they are not a good treatment choice. Liver transplant is reserved for patients with severe synthetic liver dysfunction. Patients with CF also have an increased risk of gastrointestinal tract malignancies with a third of them being hepatic or biliary tract in origin. This risk increases with age and peaks after the third decade.[35]

Primary Sclerosing Cholangitis

PSC is a chronic, progressive cholestatic liver disease of unknown cause characterized by inflammation and fibrosis of intrahepatic and extrahepatic bile ducts leading to the formation of multifocal bile duct strictures. Up to 90% of patients with PSC have underlying ulcerative colitis; however, only about 5% of patients with ulcerative colitis have PSC.[36] Many of the patients that present with PSC during childhood and adolescence do not develop symptoms suggestive of ulcerative colitis until later in life. There is a slight male predominance. About half of patients are asymptomatic at the time of presentation, or they may have nonspecific symptoms, such as fatigue and pruritus. Biochemical abnormalities include an elevated alkaline phosphatase with mildly elevated aminotransferases, and physical examination may reveal jaundice, hepatomegaly, splenomegaly, or excoriations. PSC is diagnosed by cholangiography and a liver biopsy is not always required. There is no proved treatment that slows the progression of the disease, but there are many medical and surgical therapies to treat the pruritus, strictures, and complications of PSC. Liver transplant may be considered in patients with advanced disease.

Inherited Disorders of Cholestasis

Alagille syndrome

Alagille syndrome is an autosomal-dominant inherited disease of cholestasis and is the most common disorder associated with bile duct paucity. The incidence is 1 in 100,000 live births with more than half of patients having a de novo mutation on the

JAG1 or NOTCH 2 genes.[37] There is variable penetrance and phenotypic expression. Patients are usually diagnosed as an infant when they are noted to have a direct hyperbilirubinemia, elevated aminotransferases, and a disproportionally elevated GGT. The common clinical features include chronic cholestasis; cardiac anomalies; butterfly vertebrae; posterior embryotoxon of the eye; and dysmorphic facies consisting of a triangular facies, deep-set eyes, and a broad nasal bridge. These patients may also have renal disease, pancreatic insufficiency, developmental delay, short stature, or intracranial hemorrhage. Vascular anomalies in multiple organs, including the central nervous system, are common. There is a 10% to 15% risk of intracranial hemorrhage with an associated 30% mortality. These bleeds respond well to surgical clip ligation.[38] Treatment of Alagille syndrome involves managing the different diseases in each affected organ system.

Progressive familial intrahepatic cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a heterogenous group of disorders defined by defective secretion of bile acids or other components of bile. These disorders usually present during infancy with cholestasis, coagulopathy caused by vitamin K malabsorption, elevated aminotransferases, and a normal or nearly normal GGT in PFIC 1 and PFIC 2. PFIC is associated with growth failure and progressive liver disease. PFIC 1 is autosomal-recessive and is distinguished by missense mutations in the ATP8B1 gene. Patients with PFIC 1 usually present within the first year of life, have a low or normal GGT, and have intense pruritus. The progression to biliary cirrhosis is variable but they may respond to a biliary diversion with some improvement in pruritus and a slowing of the progression of liver disease.[39]

PFIC 2 is caused by a defect in the ABCB11 gene that encodes BSEP, an ATP-dependent bile acid transporter. BSEP actively transports bile acids across the canalicular membrane into bile. Absence of BSEP function leads to a low serum GGT, low cholesterol, and chronic intrahepatic cholestasis with progression to cirrhosis usually in the first 5 to 10 years of life. Patients with PFIC 2 have about a 15% increased risk of cancer. Hepatocellular carcinoma is the most common form, but cholangiocarcinoma and pancreatic adenocarcinoma may also occur.[40]

PFIC 3 involves a mutation in the ABCB4 gene, which encodes MDR3. Absence of MDR3 results in failure of phospholipid transport into bile. Patients with PFIC 3 are noted to have a high GGT and liver biopsy shows ductal proliferation. Depending on the mutation, patients may present with clinical cholestasis in early childhood or they may present with a milder form of the disease at an older age. Pruritus is usually milder in PFIC 3, but the disease can still progress to end-stage liver disease. Treatment of patients with PFIC involves addressing nutritional deficiencies, including fat-soluble vitamin supplementation, and pruritus. Ursodeoxycholic acid might improve mild pruritis; however, severe pruritis is often refractory to medical therapy and requires surgery for biliary diversion. Biliary diversion may help the pruritis, but it might also improve biochemical abnormalities and slow the progression of liver disease. Liver transplant is a feasible option for patients with end-stage liver disease or pruritus refractory to all medical and surgical therapies.

Benign recurrent intrahepatic cholestasis is on the opposite end of the spectrum of PFIC but is caused by a mutation on the ATP8B1 gene, the same gene that causes PFIC 1. Benign recurrent intrahepatic cholestasis is an autosomal-recessive disease and is defined as intermittent episodes of cholestasis. Patients may present at any age, including adolescence, and the frequency of episodes is widely variable. During an episode, patients present with conjugated hyperbilirubinemia, pruritus, anorexia, and malaise. Each episode may last for weeks to months with a complete clinical,

biochemical, and histologic normalization. There is no treatment of benign recurrent intrahepatic cholestasis and the frequency of episodes seems to decrease with age.[39]

MANAGEMENT APPROACH TO THE ADOLESCENT WITH LIVER DISEASE

Caring for adolescents with liver disease can be far more challenging than any other age group. The clinician must juggle management of what are complex liver diseases while fully considering the patient's psychosocial health. Young people are undergoing major changes in their psychosocial and physical development while at the same time trying to gain independence during adolescence. Unfortunately, the progress in self-management skills usually lags behind psychosocial development and pediatric clinicians and parents are not always tuned in to the need to guide the adolescent's development of self-management skills. Self-management skills include adhering to the treatment regimen, taking responsibility for medications, getting required blood tests in a timely manner, scheduling and attending appointments, and recognizing signs and symptoms suggesting a change in their health status. Typically, chronologic age is frequently used as the criteria to determine the patient's readiness for a somewhat abrupt transition from child-centered health care to adult-centered health care. However, studies have shown that when responsibilities for health-related tasks are gradually shifted throughout adolescence in a developmentally appropriate manner, the adolescent gains the skills, knowledge, and experience necessary to master self-management skills and the independence required to be successful in the adult health care system.[41]

Adherence is a key component in developing self-management skills and is a universal concern when caring for adolescents. There is considerable literature discussing the psychosocial factors that predict nonadherence. Some of these factors include family interactions, psychological symptoms in the patient, barriers to adherent behavior, the disease process, level of self-management skills, care patterns including timing and frequency of medications and clinic appointments, and socioeconomic status.[42,43] However, there are strategies for improving adherence consisting of simplifying the treatment regimen; assessing and addressing common risk factors and obstacles to adherence; leveraging electronic devices to provide reminders, such as text messaging and alarms for medications; and remaining connected to the patients through more frequent follow-up.[44]

Appropriate psychosocial support is essential for any patient and family diagnosed with a liver disease, especially chronic liver disease. There is an increasing body of literature reporting symptoms of anxiety, significant stress, and posttraumatic stress disorder in patients and parents diagnosed with a perceived or actual life-threatening illness. In addition, the number of complications associated with the disease does not correlate with psychological symptoms.[45] One study reports that children with NAFLD have higher levels of depression compared with obese control subjects and the depression does not necessarily improve with standard of care measures, such as lifestyle changes and weight loss.[46] It has also been reported that chronic illnesses in childhood impact cognition and is associated with limitations in school and increased missed school days.[47] Thus, providers should consider scheduling routine follow-up for adolescents at times that do not interfere with school attendance.

Transition from pediatric-centered health care to adult-centered health care is part of a developmental process for patients with chronic childhood illnesses and requires a multidisciplinary approach. Transition of care is not the same as transfer of care, because transfer of care is only one small step in the transition of care to the adult health care system and does not mark the end of the transition process. Transition

of care should begin around 10 to 12 years depending on the developmental maturity of the patient and is a multifaceted process that addresses the medical, psychosocial, and educational needs of the adolescent as they prepare to move from pediatric-centered health care to adult-centered health care.[48] Before transfer of care to the adult health care system, the patient must achieve transfer readiness, which includes understanding the illness, self-management skills, and the ability to assume responsibility of his or her health care. In addition, it is helpful to identify an adult health care provider or group at least 6 to 12 months before the transfer and work closely with them during the transfer. This may include joint clinic appointments or scheduled appointments with the adult care provider to become familiar with the practice and expectations of the adult health care system while still following with the pediatric health care provider. Transition preparation is a continuous process and should incorporate interventions to promote self-management skills and adherence as pediatric patients prepare to move from child-centered care to adult-centered care to ensure a successful transfer of care.

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