Systemic Disease and the Liver

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Introduction

The liver is the largest parenchymal organ in the body and has a complicated circulatory system, with dual afferent blood supply .

liver mass accounts 2.5% of adult body weight, it receives nearly 25% of the resting cardiac output and at any given time contains 10–15% of total body blood volume.

The liver is also a complex metabolic organ with important functions in biosynthesis, innate immunity, metabolism and toxin/metabolite clearance.

By virtue of its size, multiple metabolic functions, and prominent position in the circulatory system, the liver is frequently involved, either as an accomplice or as an innocent bystander, in a range of systemic, circulatory and inflammatory disorders.

Hepatic Dysfunction in the Intensive Care Unit

Hepatic dysfunction is a common occurrence in the intensive care unit, affecting up to one-third of non-cirrhotic adults

acute hepatic dysfunction in the intensive care unit generally presents in one of two clinical patterns

- sepsis associated cholestasis
- hypoxic hepatitis.

The presence of hepatic dysfunction, whether manifest as sepsis-associated cholestasis or hypoxic hepatitis, is a significant factor in prognosticating short-term outcome of critically ill patients.

Sepsis-Associated Cholestasis

- Multiple pathways contribute to sepsis-associated cholestasis .

I. increased bilirubin production (hemolysis, gastrointestinal bleeding, and resorption of hematomas)
II. decreased intrahepatic bilirubin processing (shock, pharmacologic effects, use of total parenteral nutrition)
III. and/or decreased bilirubin excretion (sepsis, biliary obstruction).

Hypoxic Hepatitis

- When hepatic oxygen delivery is critically insufficient ,(due either to inadequate circulating blood volume, inadequate oxygen concentration, or impaired cellular oxygen uptake and utilization) the result is hypoxic hepatitis.

- Hypoxic hepatitis is a common cause of severe acute liver injury in hospitalized adult patients, with an incidence of **2.5–4% in adult ICUs .**
- The most common underlying disorders are acute and chronic heart failure, respiratory failure, hypovolemic shock and septic shock; less common scenarios include pericardial tamponade, prolonged seizures, heatstroke, and cardiopulmonary bypass.

Hypoxic Hepatitis

hypoxic hepatitis is characterized by a marked and rapid elevation of serum aminotransferases within 48 hours of the initial insult.

Classically, serum aminotransferase concentrations **may reach 5,000 to 10,000 IU/L, while alkaline phosphatase levels are usually normal.**

Initially, aspartate aminotransferase (AST) exceeds alanine aminotransferase (ALT), but as ALT declines more slowly, a reversal of this ratio is often seen as the levels decline.

Serum levels of **creatinine, lactate** and **lactate dehydrogenase** are often increased. **Hepatomegaly, jaundice, and coagulopathy** may be present, .

When coagulopathy is present, the timing mirrors that of aminotransferase elevation, while bilirubin levels tend to rise after aminotransferases have peaked, and are associated with a more severe clinical course and increased risk of complications .

Hypoxic Hepatitis

- Serum concentrations of AST and ALT can be expected to decrease by at least 50% within 72 hours of the insult .

- Aminotransferase level return to normal within 11 days if perfusion and oxygenation are restored and urine output is normal .

Nutritional Disorders

- The most common nutrition-related liver disease is NAFLD.
- other nutritional disorders in children in which the liver is affected :

global nutritional deficiencies

individual nutrient deficiencies and excesses, nutrition-related gastrointestinal disease,

hepatic abnormalities related to the use of dietary supplements.

CELIAC DISEASE

Liver dysfunction is one of the recognized extra-intestinal manifestations of celiac disease, and can be found in **15–54% of patients.** Liver tests (especially transaminases) should be routinely checked in all patients with CD at diagnosis.

A variety of hepatic abnormalities have been reported, including asymptomatic elevated serum aminotransferases, NAFLD, the spectrum of autoimmune liver diseases, fulminant liver failure and cryptogenic cirrhosis.

- The **most common** of these is elevated serum aminotransferases, which can be found in up to 54% of children at the time of diagnosis and may be the indication for evaluation.
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- In fact, some reports suggest that as many as **10% of all patients referred for evaluation of asymptomatic increased aminotransferases have unrecognized celiac disease** .

CELIAC DISEASE

The subsequent clinical approach is based on the pattern of the serum liver chemistry abnormalities, the clinical history, and physical findings.

The presence of both normal physical examination and hypertransaminasemia < 5 times the upper limit of normal (especially if the ratio AST to ALT is <1) in patients with confirmed CD, strongly suggest celiac hepatitis and no further evaluation is necessary before the evaluation of response to a GFD.

Both serum and histologic abnormalities improve with a gluten-free diet, usually within six months.

other etiologies should be sought and excluded if :

- patient does not respond to a gluten free diet within one year, or
- has a cholestatic pattern of liver dysfunction or
- transaminases levels >5 times upper limit of normal
- evidence of chronic liver disease at presentation and/or AST to ALT ratio >1.

Cystic fibrosis

There are multiple presentations of cystic fibrosis-related liver disease (CFLD)

- Neonatal cholestasis <10%

Conjugated hyperbilirubinemia in a neonate, often with hepatomegaly. Usually regresses within months and is not a predictor of later CFLD.

- Focal biliary cirrhosis 20 to 40%

May or may not be associated with persistently elevated aminotransferases and hepatomegaly, usually asymptomatic and developing within the first 12 years of life.

Cystic fibrosis

- Multilobular cirrhosis 5 to 10%

Advanced stage of focal biliary cirrhosis. The disease usually develops during childhood .Most such patients remain in a state of compensated cirrhosis for years or decades. May be complicated by portal hypertension (causing splenomegaly, ascites, and esophageal varices), gastrointestinal bleeding, and nutritional deficiencies. Hepatic synthetic dysfunction (coagulopathy and hypoalbuminemia) is a late and rare occurrence

Noncirrhotic portal hypertension Unknown, but this entity is well described

Portal hypertension with esophageal varices but often more than expected for the observed degree of fibrosis. If biopsy is performed, it typically shows nodular regenerative hyperplasia with missing portal veins or obliterative portal venopathy.

Cystic fibrosis

- Hepatic steatosis 10 to 60%

Incidental finding on ultrasound or liver biopsy, with transient hepatomegaly. May be seen from infancy to adolescence, and may be associated with stunting or wasting.

Steatosis may be caused by iatrogenic or environmental factors such as malnutrition, medications, essential fatty acid deficiency, and ethanol ingestion.

- Gallbladder disease associated with CF includes microgallbladder, cholelithiasis (gallstones), and cholecystitis. Evaluation and management are similar to that for patients without

Cystic fibrosis

Diagnosis — A diagnosis of CFLD is made if **two or more** of the following findings are present.

A study in adults has suggested that elastography abnormalities should be added to the criteria for adults .

- Hepatomegaly (liver span greater than the upper limit of normal [ULN] for age) and/or splenomegaly, confirmed by ultrasonography
- Abnormalities of ALT, AST, and GGT >1.5 to 2 times the laboratory upper limits of normal for >6 months, after excluding other causes of liver disease
- Ultrasonographic evidence of coarseness, nodularity, increased echogenicity, or portal hypertension, as described above
- Liver biopsy showing focal biliary cirrhosis or multilobular cirrhosis (if performed)

EVALUATION

- Annual screening for CFLD is recommended for all individuals with CF
- **Physical examination**
- **Laboratory testing** Measure platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and alkaline phosphatase at least
- **Imaging**
- ultrasonography, with or without Doppler
- Magnetic resonance elastography (MRE)
- Transient elastography

MANAGEMENT

- **Nutrition**
- **Risk reduction**

Full immunization against hepatitis A and hepatitis B

Avoid alcohol and medications with hepatotoxic side effects, including certain herbal remedies.

should be advised to avoid using nonsteroidal antiinflammatory drugs (NSAIDs) and salicylic acid to minimize risks of bleeding from portal hypertensive gastropathy, or from gastric or esophageal varices, if present

- **Ursodeoxycholic acid**

Ursodeoxycholic acid in CFLD

- Ursodeoxycholic acid (UDCA) is commonly used in the management of CFLD but has not been adequately studied, particularly regarding whether it has a role in the treatment of subclinical or other early forms of CFLD.
- Limited clinical evidence suggests that UDCA at moderate doses may improve biochemical parameters in patients with CFLD.
- However, there is no good evidence that it improves other outcomes, and indirect evidence from other cholestatic liver diseases suggest that high doses may be detrimental.
- We suggest using UDCA for children who have established cholestasis due to CFLD (eg, serum conjugated bilirubin >1 mg/dL [17.1 micromol/L]), treating with doses of 20 mg/kg/day.
- Many clinicians do not use UDCA for children with subclinical or milder forms of CFLD, but practice varies for this group of patients; there is no specific evidence that it is harmful in CF.

Congenital/Acquired Heart Disease

In children, the most common causes of heart failure are congenital heart diseases.

Among these, anomalies such as pulmonary atresia, ventricular septal defect and transposition of the great arteries may lead to pulmonary hypertension and chronic passive liver congestion.

chronic hepatic congestion is itself associated with a distinct liver lesion marked by a spectrum of fibrotic changes ranging from mild sinusoidal fibrosis to the appearance of broad fibrous septa to frank cirrhosis (cardiac cirrhosis) .

Clinically, liver injury due to chronic passive congestion is often silent.

Biochemical abnormalities may have an insidious onset, with a profile that is predominantly cholestatic, with elevations in serum gammaglutamyltransferase (GGT) and alkaline phosphatase levels out of proportion to elevations in serum aminotransferases.

Hepatic Venous Outflow Obstruction

Obstruction to outflow at any level from the small hepatic veins to the junction of the inferior vena cava (IVC) with the right atrium constitutes Budd– Chiari syndrome.

Budd–Chiari syndrome can be classified as primary when there is intraluminal obstruction by a thrombus or web, or secondary when there is extrinsic compression by an abscess, cyst or tumor.

Budd–Chiari syndrome most often presents as chronic obstruction with **hepatomegaly, ascites, abdominal distension and abdominal pain.**

In children, **lethargy and anorexia** may also be present. Often, abdominal and chest wall collaterals are prominent and distended.

Serum aminotransferase and bilirubin levels are generally only mildly to moderately elevated, although hypoalbuminemia and coagulopathy are present in almost half of patients .

Budd–Chiari syndrome

The first step in evaluation of a patient with suspected hepatic venous outflow obstruction is pulsed Doppler ultrasonography of the hepatic vessels and IVC.

Treatment :

ranges from supportive medical management of complications to liver transplantation, and depends on the site and chronicity of the obstruction, the degree of liver dysfunction, and, in children, the size of the patient .

Hematologic Disorders

Hemoglobinopathies (sickle cell anemia, thalassemia …)

The most common hemoglobinopathy is **sickle cell anemia**

- vaso-occlusive crises
- sickle cell intrahepatic cholestasis, or sickle cell hepatopathy.
- cirrhosis
- viral hepatitis
- transfusion-associated hemosiderosis
- Other unusual hepatic lesions noted in sickle cell anemia are hepatic vein thrombosis, focal nodular hyperplasia, hepatic abscesses, ischemic cholangiopathy and bilomas.

Hematologic Disorders

- Coagulation Disorders (transfusion-acquired hepatotropic viruses)
- Leukemia and Lymphoma (tumor infiltration, intrahepatic or extrahepatic biliary obstruction, malignancy-associated hemophagocytic syndrome, opportunistic infections, and hepatotoxic drugs)
- Allogeneic Stem Cell Transplantation (primary disease, drug-induced liver injury, infectious, vascular, parenteral nutrition-associated, immunologic)

Collagen Vascular Disease

- Hepatomegaly, splenomegaly, biochemical abnormalities, and/ or histologic changes are commonly found in the setting of the various collagen vascular disorders

- primary manifestation of the disease itself, related to immune-mediated injury, or secondary to drug toxicity or fatty infiltration.

Collagen Vascular Disease

Juvenile Idiopathic Arthritis

Hepatomegaly and splenomegaly are common in children with juvenile idiopathic arthritis (JIA), affecting 10–15% ,**more frequently in those with systemic JIA (sJIA),** particularly when complicated by macrophage activation syndrome .

Asymptomatic elevations in serum aminotransferases unrelated to muscle injury may occur, in which correlate with disease activity, and rarely lead to progressive liver injury.

Other, specific causes of liver dysfunction in patients with JIA include **drug toxicity (41%** of those with liver dysfunction), **fatty liver (6%), viral hepatitis (1–2%), primary biliary cirrhosis (4%),** and **autoimmune hepatitis (1–2%) .**

Collagen Vascular Disease

Systemic Lupus Erythematous

More than one-third of patients with SLE have some elevation in serum aminotransferase or gammaglutamyltransferase levels, while **40%** have clinically detectable **hepatomegaly** .

The most common cause of liver dysfunction in patients with SLE is drug-induced liver injury (31%),

followed by primary liver involvement with the disease itself (lupus-associated hepatitis; 29%), fatty liver (18%), autoimmune hepatitis (5%), primary biliary cholangitis (2%), and primary sclerosing cholangitis (1.6%).

Portal vein thrombosis ,Budd–Chiari syndrome and hepatic VOD/SOS can also occur in the setting of SLE, usually due to the co-existence of the antiphospholipid syndrome .

Collagen Vascular Disease

- Miscellaneous Disorders
  - Sjögren syndrome, systemic sclerosis, dermatomyositis, mixed connective tissue disease and Behçet disease may all be associated with liver dysfunction of varying incidence.

  - **Kawasaki disease :**
  - hydrops of the gallbladder, hepatomegaly, elevated serum aminotransferases, and clinical jaundice.

Endocrine Disorders

- Hypopituitarism
  - pituitary hormones,particularly adrenocorticotropic hormone and thyroid-stimulating hormone, play a role in the regulation of bile acid secretion and bile flow.
- Thyroid Disorders
  - Abnormalities in serum aminotransferase levels are reported in 27–44% of children and adults with hyperthyroidism and may present with a hepatocellular or a cholestatic pattern.
  - Reversible abnormalities in liver biochemistries are also common in hypothyroidism. some studies report hypothyroidism as an independent risk factor for the presence and severity of NAFLD.
  - Myopathy associated with hypothyroidism may lead to increased serum aminotransferase levels of muscle origin, with no hepatic contribution
  - There is an association between autoimmune thyroid disease and primary autoimmune liver disease .

Endocrine Disorders

- Adrenal Disorders

Outside of the neonatal period, mildly elevated aminotransferases have been described in association with adrenal insufficiency (Addison disease)

excess of adrenocorticoid hormones, whether exogenous or endogenous (Cushing disease/syndrome), is far more likely to be associated with hepatic complications (metabolic syndrome).

Endocrine Disorders

Diabetes Mellitus

liver dysfunction may be found in up to one-third of patients with diabetes.

The spectrum of histopathologic lesions includes increased hepatocyte glycogen, hyalin deposition, steatosis, and fibrosis leading to cirrhosis.

- most common manifestation of liver disease in diabetes is NAFLD .

-Mauriac syndrome is the complication most unique to children. This syndrome occurs in children with uncontrolled type 1 diabetes and is characterized by severe growth failure, hepatomegaly, pubertal delay and Cushingoid features.

THANKS FOR YOUR ATTENTION