Liver and biliary disease in childhood

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Abstract

Acute liver disease or failure in children is the result of viral hepatitis (A, B, E, seronegative), indeterminate hepatitis or inherited metabolic liver disease. The clinical presentation includes jaundice, coagulopathy and encephalopathy. Uncomplicated acute hepatitis resolves spontaneously, but progressive acute liver failure is fatal in 70% of cases and requires referral to specialized units to prevent complications and for consideration for liver transplantation. Chronic liver disease can result from unresolved neonatal liver disease caused by either inherited cholestasis or α_1-antitrypsin deficiency. Chronic viral hepatitis B and C are rare but significant diseases for which there is now effective therapy. Treatment for hepatitis B is still evolving, but the new direct-acting antivirals for hepatitis C are highly successful in children as well as adults, although licensed therapy is only available for children <12 years of age, while clinical trials continue for younger children. In older children, autoimmune liver disease, non-alcoholic steatohepatitis and cystic fibrosis are the most common causes. Treatment includes specific medication, nutritional support and liver transplantation for end-stage disease. The long-term outcome of liver transplantation is excellent, >80% surviving for 15–20 years with good quality of life as adults.

Keywords Hepatitis; liver failure; MRCP; paediatric liver disease; paediatric liver transplantation; transition to adult services

Key points

- Children with acute or chronic liver disease can present without jaundice, and it is important to perform a full range of liver function tests to make the diagnosis
- Cirrhosis caused by any form of liver disease including autoimmune disease can present with growth failure, so liver disease needs to be excluded when investigating such children
- The increase in obesity in childhood means that non-alcoholic liver disease is a common cause of elevated transaminases and significant liver disease
- The improved diagnosis and management of children with liver disease means that all adult physicians should be aware of the causes of paediatric liver disease and the need for long-term follow-up
- Transition to adult care requires a different coordinated approach within a multidisciplinary team

Introduction

In contrast to neonates, older children with liver disease may not be jaundiced. The clinical presentation varies from acute hepatitis to insidious development of hepatosplenomegaly, portal hypertension and malnutrition.

Acute liver disease

Viral hepatitis, indeterminate hepatitis, autoimmune hepatitis and metabolic liver disease are the most common acute liver diseases in children.

Acute viral hepatitis: the causative agents are hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis E virus (HEV), Epstein–Barr virus (EBV) and cytomegalovirus (CMV). Acute hepatitis C virus (HCV) is unusual in childhood but should be excluded.[1]

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Many children are asymptomatic and anicteric, and most episodes of hepatitis are never recognized. In symptomatic cases, vomiting, abdominal pain, lethargy and jaundice are common symptoms.

Diagnosis – serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations can be elevated to 10–100 times normal in acute viral hepatitis. Serum alkaline phosphatase can be moderately elevated (e.g. 2.5 times normal).

Immunoglobulin (Ig) M antibodies to HAV, HEV and CMV, hepatitis B core antigen and antibodies to EBV early capsid antigen are present in the serum. Measurement of viral DNA (HBV, CMV, EBV) or RNA (HAV, HEV, HCV) allows rapid diagnosis. Antibodies to HCV are not present until 12–26 weeks after the onset of jaundice. However, HCV infection can be confirmed by polymerase chain reaction (PCR) analysis within 4 days of infection.

Liver biopsy is not required for diagnosis unless there are complications. Centrilobular necrosis and inflammation are typical histological changes.

Management – uncomplicated acute hepatitis is managed at home. Hospital admission is necessary only when the child suffers severe vomiting, abdominal pain or lethargy, coagulation is prolonged, or transaminase activity remains high. Fulminant hepatitis occurs in <5% of cases, but abnormal coagulation is an early sign. Neither hepatitis A nor E becomes chronic but, as in adults, hepatitis B and hepatitis C can progress to chronic hepatitis or cirrhosis. CMV and EBV hepatitis seldom lead to cirrhosis.

Paracetamol overdose: this is rare in childhood, but a minority progress to acute liver failure, particularly if other drugs or alcohol have been ingested.

Acute liver failure (Table 1**):** acute liver failure can occur at any age. In the developed world, seronegative or indeterminate

Aetiology of acute liver failure in children

Causes	Investigations
Infection	
• Viral hepatitis A, B, C, E	Viral serology
• Epstein–Barr virus	
• Cytomegalovirus	
Indeterminate hepatitis	By excluding other causes
Poison/drugs	
• Paracetamol	Plasma paracetamol
• Isoniazid	
• Halothane	Halothane antibodies
• Valproate[a]	
Autoimmune hepatitis	Autoimmune screen
Metabolic	
• Wilson's disease	Copper, ceruloplasmin
• Tyrosinaemia type 1	Urinary succinylacetone
Mitochondrial disease	Microvesicular fat in liver
	Urinary dicarboxylic acids

[a] Liver contains microvesicular fat because of abnormalities in fatty acid oxidation.

Table 1

hepatitis is the leading cause.[2] The syndrome always includes encephalopathy and coagulopathy. Jaundice can be a late feature.

Assessment – the typical findings in acute liver failure are:

- ALT and AST activity usually high (10 times normal)
- prothrombin time >40 seconds
- plasma ammonia >100 mmol/litre
- slow rhythm with triphasic waves on electroencephalography
- computed tomography (CT)/magnetic resonance imaging (MRI) features of cerebral oedema.

The patient should be referred to a centre where transplantation can be performed if any of the following features are present:

- prothrombin time >60 seconds
- rising serum bilirubin (>300 micromol/litre)
- decreasing serum transaminases without clinical improvement (reduced hepatic reserve)
- decreasing liver size
- metabolic acidosis (pH <7.3)
- hypoglycaemia (glucose <4 mmol/litre)
- serum creatinine >300 micromol/litre
- hepatic coma grade 2 or more.

Management – intensive care support includes prevention of gastrointestinal haemorrhage with proton pump inhibitors, maintenance of plasma glucose >4 mmol/litre with intravenous glucose, prevention of sepsis with broad-spectrum antibiotics and antifungal therapy, treatment of coagulopathy with fresh frozen plasma and vitamin K, and management of cerebral oedema with fluid restriction, mannitol 0.5 g/kg intravenously and elective hyperventilation. Intracranial pressure monitoring is no longer standard therapy. Plasmapheresis is occasionally beneficial in younger children.

It is important to exclude potentially treatable causes of acute liver failure such as autoimmune hepatitis, Wilson's disease and tyrosinaemia type I, and to treat with *N*-acetylcysteine in paracetamol poisoning. The prognosis is worse in children with metabolic disease or indeterminate hepatitis.

Liver transplantation should be performed before irreversible brain damage caused by cerebral oedema or hypoglycaemia develops. Without transplantation, 70% of children die.

Valproate poisoning: this form of acute liver failure usually occurs in children <2 years of age. It can also occur with other anticonvulsants. Underlying mitochondrial disease is a risk factor. Liver histology shows microvesicular steatosis, and DNA analysis for the POLG genes may be positive.

Management is as for acute liver failure. Milder cases recover but liver transplantation is contraindicated because of progressive neurological disease.

Chronic liver disease

Chronic viral hepatitis: Hepatitis B: 90% of infants infected with HBV at birth and 10% of infants infected by other family members become chronic carriers. There is an increase in infants infected perinatally because of failure of vaccination or high maternal viral load. Diagnosis depends on the following features[1]:

- hepatitis B surface antigen (HBsAg)-positive for >6 months
- hepatitis B e antigen-positive
- elevated HBV DNA
- chronic hepatitis with HBsAg in hepatocytes on histology.

Liver function tests can be normal. Most children are asymptomatic and grow and develop normally. Cirrhosis develops in 10% of cases. Hepatocellular carcinoma can develop, and annual ultrasonography and monitoring of serum α-fetoprotein (AFP) are advisable to enable early diagnosis.

Management – it is important to treat the child normally and encourage schools and nurseries to treat them as any other child. All normal activities and sports are permitted, but carers (and older children) need to be aware of how to handle cuts and injuries as well as close contact with others.

Interferon-α therapy for chronic infection was successful in 30–50% of children, but is no longer used. Recent trials with pegylated interferon (with or without a nucleoside inhibitor) has not demonstrated sufficient efficacy and is not recommended.

Oral antiviral therapy (lamivudine, adefovir, tenofovir, entecavir) reduces HBV DNA in 90% of children; the seroconversion rate is about 25%, but development of viral resistance to lamivudine prevents its long-term use. Clinical trials of adefovir have not shown benefit and it is not recommended except to treat lamivudine resistance. Entecavir is now licensed for children >2 years of age. Tenofovir disoproxil fumarate is licensed for HIV and in adolescents with HBV. Telbivudine is being evaluated.

Hepatitis C: children with hepatitis C are asymptomatic, but recent data indicated that 30% develop cirrhosis within 30 years of infection, indicating the need to identify carriers and treat early.[3] Currently, most children are infected by vertical transmission.

Diagnosis – this depends on the detection of antibodies to HCV and is confirmed by the presence of HCV RNA on PCR

analysis (because passive transfer of maternal antibodies can last for up to 12–18 months). Liver biopsy is not unless there are co-morbidities, and histology usually demonstrates mild hepatitis with fatty change.

Management – although children responded better than adults to treatment with pegylated interferon and ribavirin, this therapy is no longer indicated because of the efficacy of the new direct-acting antivirals in children. Currently three drugs (Sovaldi, Harvoni and glecaprevir/pibrentasvir) are licensed for adolescents, and clinical trials are in progress for children <12 years of age.

Autoimmune hepatitis: autoimmune hepatitis is more common in girls than in boys (3:1). There are two forms: type 1 (antinuclear antibody- and smooth muscle antibody-positive) and type 2 (liver–kidney microsomal antibody-positive). The clinical presentation varies from acute hepatitis with autoimmune features to an insidious development of cirrhosis, portal hypertension and malnutrition.[4]

Diagnosis – this can be made from the following observations:

- positive non-organ-specific autoantibodies (Table 2) in 70% of patients, although these can be negative at onset
- raised immunoglobulins (IgG >20 g/litre)
- reduced serum C3 and C4 complement
- elevated transaminase activity
- reduced albumin and prolonged coagulation
- chronic hepatitis with portal inflammation, piecemeal necrosis and bridging fibrosis on liver histology.

Management – most children respond to prednisolone 2 mg/kg, and azathioprine 2 mg/kg, although approximately 20% require transplantation despite second-line therapy with ciclosporin, tacrolimus or mycophenolate mofetil. Withdrawal of immunosuppression after 12–18 months of treatment is seldom successful. Children with type 2 disease have a worse prognosis and are more likely to require liver transplantation. Life-long follow-up is required as the disease can recur after transplantation.

Primary sclerosing cholangitis: some children with autoimmune hepatitis have associated primary sclerosing cholangitis or ulcerative colitis. The abnormal bile ducts and dilated gallbladder are demonstrated by magnetic resonance cholangiopancreatography (MRCP). Histology confirms chronic hepatitis with sclerosis of bile ducts, sometimes referred to as 'overlap syndrome', but this is now thought to be part of the spectrum of sclerosing cholangitis. Unlike adults, children can initially respond to immunosuppression and ursodeoxycholic acid (UDCA) 20 mg/kg. The long-term prognosis is for progression to biliary cirrhosis, usually in adult life.

Wilson's disease: Wilson's disease is an autosomal recessive disorder in which copper accumulates in the liver, brain, kidney and cornea. It is discussed elsewhere in this issue (see pages 814–817 of this issue).

Cystic fibrosis (CF): liver disease, ranging from fatty liver to cirrhosis and portal hypertension, occurs in 20% of adolescents with CF, more commonly in male patients. The aetiology is unknown; the regulator receptor is found on biliary cells and can be associated with abnormal acid concentrations. Early liver disease is difficult to detect because jaundice is a late feature, but it is suggested by a raised alkaline phosphatase or γ-glutamyl transpeptidase, a transient increase in serum transaminases, a heterogeneous liver on ultrasonography, or fatty infiltration, focal biliary fibrosis or secondary biliary cirrhosis on liver histology.

Management is supportive and involves nutritional therapy, particularly vitamin A and E supplementation, and UDCA 20 mg/kg. Liver transplantation is indicated in end-stage liver failure but not for portal hypertension. Lung function can improve after transplantation, but late deaths are related to CF lung disease.

Metabolic liver disease: α_1-Antitrypsin deficiency and tyrosinaemia type 1 can present late in childhood with cirrhosis and portal hypertension. Tyrosinaemia type 1 should respond to treatment with nitisinone (NTBC).

Congenital hepatic fibrosis: The spectrum of fibropolycystic disease includes congenital hepatic fibrosis, polycystic kidneys with hepatic fibrosis/cysts and congenital intrahepatic biliary dilatation (Caroli's disease) with or without renal cysts. Liver function tests can be normal. Endoscopic retrograde cholangiopancreatography or MRCP confirms abnormal bile ducts

Diagnostic features of chronic liver disease in older children (>2 years)

Chronic liver disease	Diagnostic investigations
Chronic hepatitis	Portal inflammation
Hepatitis B, C, D, EBV, CMV	Serology
Autoimmune hepatitis type 1 or 2	IgG >20 g/litre, reduced C3 and C4 complement, antinuclear antibodies and smooth muscle antibodies (type 1) Liver–kidney microsomal antibodies (type 2)
Primary sclerosing cholangitis	ERCP/MRCP, liver biopsy
Wilson's disease	Serum copper Caeruloplasmin Urinary copper
α_1-Antitrypsin deficiency	Serum α_1-antitrypsin and phenotype
Cystic fibrosis	Sweat test, liver biopsy, mutations
Cryptogenic cirrhosis	Liver biopsy
Non-alcoholic fatty liver disease	Fatty change on liver biopsy/ultrasound
Tyrosinaemia type 1	Urinary succinylacetone, fumaryl acetoacetate in fibroblasts
Hereditary fructose intolerance	Fructose 1,6-phosphate aldolase mutations in liver, reducing sugars in urine

ERCP, endoscopic retrograde cholangiopancreatography; Ig, immunoglobulin; MRCP, magnetic resonance cholangiopancreatography.

Table 2

and biliary cysts. Histology demonstrates hepatic fibrosis with abnormal bile ductules, but the hepatic parenchyma is normal.

Management of hepatic disease relates mainly to treatment of portal hypertension. The prognosis depends on the severity of renal disease, portal hypertension and recurrent cholangitis. If both liver and renal failure develop, combined liver and kidney transplantation is indicated.

Non-alcoholic steatohepatitis: Increased childhood obesity and recognition of insulin resistance in several inherited disorders has led to diagnosis of this disorder in childhood. Most children are asymptomatic, although cirrhosis has been reported in syndromic forms of non-alcoholic fatty liver disease. The long-term outcome is not determined, but it is likely that the cirrhosis, cardiac disease and diabetes will develop in adult life. Children respond poorly to weight reduction and exercise. Metformin, vitamin E and UDCA have not proved effective. The use of gastric bands has not been universally accepted in childhood.

Cirrhosis: Chronic liver disease often leads to cirrhosis, which can be compensated (maintained hepatic function, growth and development) or decompensated (many complications, retarded growth and development).

Clinical features – children with decompensated cirrhosis have palmar and plantar erythema, telangiectasia, malnutrition, hypotonia and hepatosplenomegaly with ascites (Figure 1). Jaundice can be absent.

Diagnosis – although cirrhosis is a histological diagnosis (extensive fibrosis, regenerative nodules), it is generally associated with:

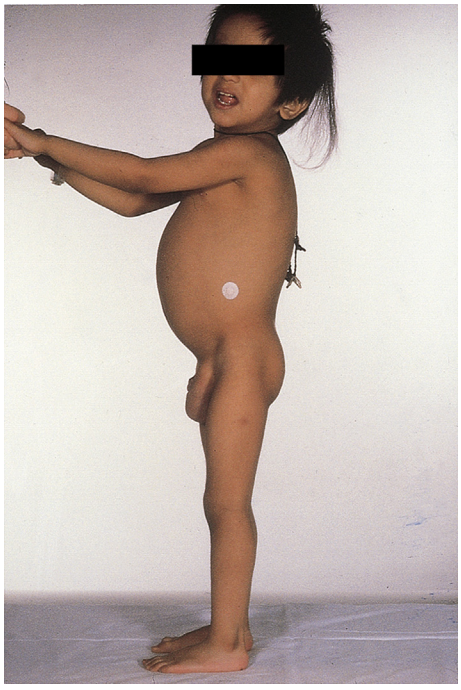

Figure 1 This boy has chronic neonatal liver disease and has developed cirrhosis and portal hypertension. Note the distended abdomen and malnutrition with loss of fat stores and muscle bulk. He has also suffered pathological fractures from metabolic disease.

- echogenic liver, splenomegaly and varices on ultrasonography
- abnormal FibroScan measurements
- oesophageal and gastric varices on endoscopy
- mild transaminitis
- increased serum alkaline phosphatase and γ-glutamyl transpeptidase (twice normal)
- low serum albumin (<30 g/litre)
- low serum calcium and phosphate secondary to rickets
- anaemia
- prothrombin time >20 seconds
- slow, irregular low-frequency waves on electroencephalography in patients with associated encephalopathy.

Management – dietary management of older children is difficult. A high-calorie protein feed (110–150% recommended daily allowance) is required. Protein restriction is not advised unless encephalopathy is severe. Medium-chain triglycerides (triacylglycerols) are supplemented to 50% of fat intake, and fat-soluble vitamin supplementation is required. Nocturnal nasogastric feeding is usually required.

Encephalopathy is treated with lactulose 2–4 ml/kg per day in three doses, or rifaximin 20–30 mg/kg per day (split into either two or three doses per day). Ascites is managed by fluid restriction and diuretic therapy (spironolactone 3 mg/kg, or furosemide 1 mg/kg). Bleeding oesophageal varices are managed using oesophageal banding or insertion of a transjugular intrahepatic portosystemic shunt. Pruritus is alleviated by rifampicin 3 mg/kg, UDCA 20 mg/kg, colestyramine 0.5 g/kg/day, or topical evening primrose oil.

Without transplantation, most children die before adolescence. Hepatocellular carcinoma is a long-term risk in adult life.

Liver tumours: Metastases from other tumours (e.g. neuroblastoma, Wilms' tumour, lymphoma, leukaemia) are more common than primary tumours. Primary liver tumours include hepatoblastoma (64%, most common in children <5 years of age), hepatocellular carcinoma (27%) and mesenchymal tumours (9%). Patients usually present with painless abdominal swelling.

Diagnosis is confirmed by:

- AFP 1–10,000 IU/litre in hepatoblastoma and 1–2000 IU/litre in hepatocellular carcinoma
- a hepatic mass defined by ultrasonography, CT or MRI
- histology.

Management comprises surgical resection preceded by chemotherapy. Liver transplantation is indicated in those with an unresectable tumour without extrahepatic metastases. Postoperative chemotherapy is recommended. The prognosis has improved (5-year survival >80%).

Liver transplantation

Liver transplantation is indicated in patients with acute or chronic liver failure, metabolic liver disease or hepatic tumour. Transplantation should be considered in those with:[5]

- conjugated bilirubin >120 micromol/litre
- prothrombin time >20 seconds
- decreasing albumin <30 g/litre
- persistent encephalopathy
- recurrent hepatic complications that do not respond to medical therapy

- diminishing quality of life
- malnutrition
- delayed development.

Irreversible extrahepatic disease (usually cardiac or neurological) is the only absolute contraindication to transplantation. Organs are matched by blood group and size. Reduction hepatectomies (in which a larger liver is cut down to fit a smaller child) and split-liver grafting (one liver is used for two recipients) have lessened problems resulting from the shortage of paediatric donor livers. Living-related transplantation is an increasing viable alternative.

Prognosis — 1-year survival is 90—95% and 20-year survival >80%. Morbidity is high initially; sepsis (70%), rejection (60%), vascular thrombosis (10%) and biliary complications (20%) can occur. Life-long follow-up is required to monitor immunosuppression and prevent post-transplantation lymphoproliferative disease, renal dysfunction and hypertension, although the development of less toxic immunosuppression has reduced these complications. Long-term data on survivors indicate that normal growth, development and puberty are achieved and that quality of life is good.

Transition to adult services

The increasing survival of children with liver disease and after transplantation means that significant numbers transition to adult services. These young people with a lifetime of chronic illness are best served by adult hepatologists with an interest in adolescence, supported by a multidisciplinary team. Adequate support through transition can reduce non-adherence to medication and hospital clinics. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 6-year-old child presented with a 3-day history of being unwell; he had not been eating normally, was sleepy and had been vomiting with no diarrhoea.

On clinical examination, he was irritable and jaundiced and had a large tender liver but no splenomegaly.

What is the most likely diagnosis?

A. Hepatitis C
B. Chronic neonatal liver disease
C. Non-alcoholic fatty liver disease
D. Acute fulminant hepatitis
E. Cystic fibrosis liver disease

Question 2

An 11-year-old girl presented acutely with a history of vomiting bright red blood associated with some vague abdominal pain. She had been passing dark stools for the previous few days. She had a history of neonatal liver disease.

On clinical examination, she was pale, sweaty and jaundiced, with a heart rate of 110 beats/minute. The liver appeared reduced in size on percussion, and the spleen was markedly enlarged.

Investigations

- Haemoglobin 60 g/litre (115—155)

What is the best immediate management?

A. Send her for an ultrasound examination to confirm the size of the spleen
B. Take a detailed history of recent food ingestion
C. Admit her immediately to the paediatric intensive care unit
D. Start intravenous antibiotics and proton pump inhibitors
E. Resuscitate her with packed cells and fluids, and arrange emergency endoscopy