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 or sero-negative), 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 may result from unresolved neonatal liver disease, due to 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 are highly successful in adults with hepatitis C and will soon be in clinical trials in children. In older children, autoimmune liver disease, non-alcoholic steatohepatitis or cystic fibrosis are the commonest causes. Treatment includes specific medication, nutritional support and liver transplantation for end-stage disease. The long-term outcome of liver transplantation is excellent, more than 80% surviving for 15–20 years with good quality of life, although outcomes following transition to adult services could be improved.

Keywords hepatitis; liver failure; paediatric liver disease; paediatric liver transplantation; transition to adult services

What's new?

- Rapid development in molecular and genetic techniques has improved our ability to diagnose many forms of inherited liver disease and led to the development of better therapy
- Availability of new drugs for viral hepatitis mean that it is important to screen for hepatitis B and C
- The obesity epidemic has led to an increase in children with non-alcoholic steatohepatitis which responds poorly to therapy and will be an increasing burden on adult liver services
- Centralization of paediatric liver services, liver surgery and liver transplantation in the UK has improved diagnosis, management and outcome for children
- Adolescent transition to adult services are associated with poor outcomes because of non-adherence

In contrast to neonates, older children with liver disease may not be jaundiced.[1] 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.[2] 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.

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Diagnosis – serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity may be elevated by 10–100 times the normal concentration in acute viral hepatitis. Serum alkaline phosphatase may be moderately elevated (e.g. 2.5 times normal). Immunoglobulin M (IgM) antibodies to HAV, HEV, CMV, hepatitis B core antigen and antibodies to EBV early capsid antigen are present in the serum. Measurement of viral DNA (HBV, CMV and EBV) or RNA for HAV, HEV and HCV allow 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 less than 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 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, sero-negative or indeterminate hepatitis is the leading cause.[3] The syndrome always includes encephalopathy and coagulopathy. Jaundice may be a late feature.[3]

Assessment – the typical findings in acute liver failure are:

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

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 exclusion of other causes
Poison/drugs	
• Paracetamol	Plasma paracetamol
• Isoniazid	
• Halothane	Halothane antibodies
• Valproate[a]	
Autoimmune hepatitis	Autoimmune screen
Metabolic	
• Wilson's disease	Copper, caeruloplasmin
• Tyrosinaemia type 1	Urinary succinylacetone
Reye's syndrome	Microvesicular fat in liver
	Urinary dicarboxylic acids

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

Table 1

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

- prothrombin time over 60 seconds
- rising serum bilirubin (>300 μmol/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 μmol/litre
- hepatic coma grade II or more.

Management – intensive care support includes prevention of gastrointestinal haemorrhage with proton pump inhibitors, maintenance of plasma glucose to more than 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 (IV), elective hyperventilation and intracranial pressure monitoring. Occasionally in younger children, plasmapheresis may be beneficial.

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 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 under the age of 2 years. It may 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 a rise in infants infected perinatally due to failure of vaccination or high maternal viral load. Diagnosis depends on the following features:[4]

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

Liver function tests may be normal. Most children are asymptomatic and grow and develop normally. Cirrhosis develops in 10% of cases. Hepatocellular carcinoma may 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 (IFN-α) therapy for chronic infection is successful in 30–50% of children. Improvement is indicated by clearance of HBeAg and, rarely, by clearance of HBsAg. The dose is 6 MU/m^2 given three times per week by subcutaneous injection for 6 months. Pegylated interferon is currently being evaluated in children and on a practical basis has replaced interferon. Oral antiviral therapy (lamivudine, adefovir, tenofovir, and 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 did not show benefit and it is not recommended except to treat lamivudine resistance. Entecavir, and tenofovir have recently completed clinical trials and telbivudine is being evaluated.

Hepatitis C: children with hepatitis C are asymptomatic and do not develop significant disease until adult life. Following effective screening programmes, most children are now infected by vertical transmission.[5]

Diagnosis depends on detection of antibodies to HCV and confirmed by the presence of HCV RNA on PCR analysis (because passive transfer of maternal antibodies may last for up to 12–18 months). Liver biopsy is indicated in patients for whom treatment is being considered and histology usually demonstrates mild hepatitis with fatty change.

Management – children respond better than adults to treatment with pegylated interferon and ribavirin, which achieves a sustained response in 70% of children (>90% in children with genotype 2 or 3).[6] Guidelines for future trials in both hepatitis B and C have been agreed with the European Medicines Agency