Liver and biliary disease in childhood

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Abstract

Acute liver disease or failure in children is most often due to viral hepatitis (A, B, E or sero-negative), paracetamol overdose 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 be due to unresolved neonatal liver disease, either inherited cholestasis or α_1-antitrypsin. Chronic viral hepatitis B and C are rare but significant diseases, which require family support and long-term monitoring. Treatment for hepatitis B remains unsatisfactory, but combination therapy for hepatitis C is successful in over 70% of children. In older children, autoimmune liver disease or cystic fibrosis is the commonest causes, but non-alcoholic steatohepatitis is also common. 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 with good quality of life.

Keywords hepatitis; liver failure; paediatric liver disease; paediatric liver transplantation

What's new?

- Rapid development in molecular and genetic techniques has improved our ability to diagnose many forms of inherited liver disease, providing much needed insight into hepatic pathophysiology
- The obesity epidemic has meant that children develop non-alcoholic steatohepatitis, related insulin resistance, metabolic syndrome and a number of inherited syndromes
- Centralization of paediatric liver services, liver surgery and liver transplantation in the UK has improved diagnosis, management and outcome for children

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

Acute viral hepatitis

The causative agents that must be considered include hepatitis A virus (HAV), hepatitis B virus (HBV), epidemic hepatitis E virus (HEV) infection, Epstein–Barr virus (EBV) and cytomegalovirus (CMV), and sero-negative hepatitis. 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.

Diagnosis – serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity may be elevated by 10–100 times the normal level in acute viral hepatitis. Serum alkaline phosphatase levels 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 and polymerase chain reaction (PCR) tests are now available. Antibodies to HCV are often not present until 12–26 weeks after the onset of jaundice. However, HCV infection can be confirmed by 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 C hepatitis may 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 has been ingested.

Acute liver failure (Table 1)

Acute liver failure can occur at any age. 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.

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 bilirubin (>300 μmol/litre)

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Her research interests include pathophysiology of liver development, molecular genetics of inherited liver disease, and quality and outcome of life following liver transplantation. Competing interests: none declared.

Aetiology of acute liver failure in children

Causes	Investigations
Infection	
• Viral hepatitis A, B, C, E, undefined	Viral serology
• Epstein–Barr virus	
• Cytomegalovirus	
Poison/drugs	
• Paracetamol	Paracetamol level
• Isoniazid	
• Halothane	Halothane antibodies
• Valproate[a]	
Autoimmune hepatitis	Autoimmune screen
Metabolic	
• Wilson's disease	Copper, ceruloplasmin
• 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

- decreasing serum transaminases without clinical improvement (reduced hepatic reserve)
- decreasing liver size
- metabolic acidosis (pH <7.3)
- hypoglycaemia (glucose <4 mmol/litre)
- 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.

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 sero-negative 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. It is now known to be a mitochondrial disorder. Liver histology shows microvesicular steatosis. Liver transplantation is contraindicated because of progressive neurological disease.

Management is as for acute liver failure. Liver transplantation may be required; mortality exceeds 50%.

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. Diagnosis depends on the following features:[4]

- hepatitis B surface antigen (HBsAg) positive for more than 6 months
- hepatitis B e antigen (HBeAg) positive
- 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 – integration of the child into school and society is essential. 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 has not yet been evaluated in children. Oral lamivudine reduces HBV DNA in 90% of children; the seroconversion rate is 25%, but development of *YMDD* mutants prevents its long-term use. Clinical trials of adefovir did not show benefit and it is not recommended except to treat lamivudine resistance. Entecavir, telbivudine and tenofovir are 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 usually demonstrates mild hepatitis with fatty change.

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

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 insidious development of cirrhosis, portal hypertension and malnutrition.[6]

Diagnosis – a diagnosis of autoimmune hepatitis can be made from the following observations:

- 70% of patients are positive for non-organ-specific autoantibodies (Table 2) but may be negative at onset
- raised immunoglobulins (IgG >20 g/litre)
- reduced serum C3 and C4 complement
- elevated transaminase activity