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SUMMER SCHOOL: PEDIATRIC HEPATOLOGY

Acute liver failure in children and adolescents

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Summary Acute liver failure is a severe and sudden onset of hepatocyte dysfunction, leading on to synthetic and detoxification failure, which could progress to multi-organ failure and death. Common causes vary with age and geographical location. Metabolic liver diseases are frequent in the young child, sometimes amenable to a specific treatment or prenatal diagnosis. In older children, viruses, toxics, metabolic diseases (especially Wilson), autoimmune hepatitis are the main causes. Management should be initiated in conjunction with investigations, as soon as liver failure is diagnosed. The patients should be early transferred to an expert centre, where complications can be prevented and liver transplantation is possible. Improved intensive care management and availability of donor organs (split livers or living-related donors) has made it possible to transplant young children, and improved their survival chances.

Highlights

- The highest incidence of acute liver failure is seen in newborns.
- Acyclovir should be started in all neonates with liver failure, as herpes virus infection is the predominant viral cause.
- In adolescents, the main cause is toxic.
- Encephalopathy is not easy to recognize in young children. EEG changes are seen before clinical symptoms.

Definition

Acute liver failure (ALF) is rare in children but carries high mortality. As the onset of disease might be in utero and difficult to establish, Bhaduri and Vergani defined ALF in children as ''a rare multisystem disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis in a patient with no recognized underlying chronic liver disease''. The Paediatric Acute Liver Failure (PALF) study group used the following criteria:

- hepatic-based coagulopathy defined as a prothrombin time (PT) greater than or equal to 15 seconds or international normalized ratio (INR) greater than or equal to 1.5 not corrected by vitamin K, in the presence of clinical hepatic encephalopathy (HE), or a PT greater than or equal to 20 seconds or INR greater than or equal to 2.0 regardless of encephalopathy (HE);
- biochemical evidence of acute liver injury;
- no known evidence of chronic liver disease.

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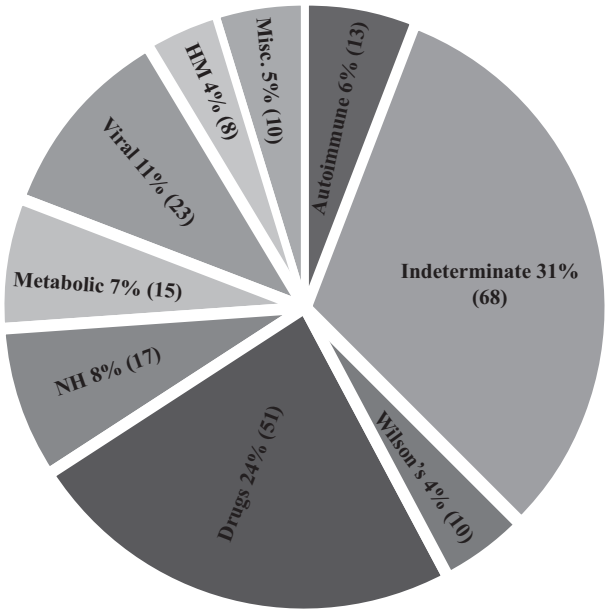

Figure 1 Aetiology of acute liver failure in 215 consecutive children who presented to King's College Hospital, London.

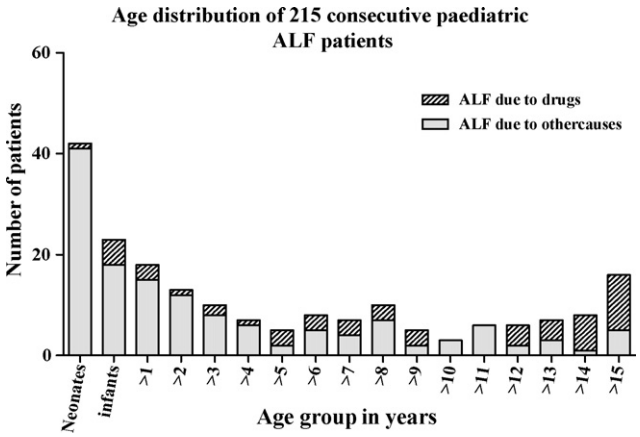

Figure 2 Age distribution of 215 consecutive children presented to King's College Hospital, London (1990—2003). Highest rate of occurrence of acute liver failure (ALF) is during neonatal period, and during adolescence predominant cause of ALF is drugs.

Coagulopathy

The synthesis of coagulation factors are affected at different rates depending on the degree of liver failure, and measurement of them could act as prognostic markers. Due to defective synthesis and impaired clearance of procoagulant/anticoagulant factors, a degree of intravascular coagulation (IC) invariably exists in ALF, and can progresses to fulminant disseminated intravascular coagulation when there is associated infection or bleeding.

Aetiology

It varies with age and geographical location: viral hepatitis is the most common in south East Asia and Latin America, in Northern America and Europe, the aetiology remains indeterminate. Though the exact frequency of ALF in children is unknown, incidence of ALF in USA is around 5.5/million/year among all ages (Figs. 1 and 2).

Viral hepatitis

Water-borne viral hepatitis (A and E) is the most common cause in developing countries. With hepatitis A virus (HAV), the risk of ALF is 0.1 to 0.4%, with hepatitis E, it is 0.6 to 2.8% in adults, it maybe increased during pregnancy. The ALF due to hepatitis B virus (HBV) can occur at the time of acute infection, reactivation of a chronic HBV infection, or seroconversion from a hepatitis B e antigen — positive to a hepatitis B e antibody (HBeAb)-positive state. Infants born to HBeAb positive mothers are at special risk between 6 weeks to 9 months. Super infection or co-infection of HBV-infected patients with delta virus (HDV) can cause liver failure. Hepatitis C virus (HCV) infection has not been reported as a cause of ALF.

Members of the herpes virus family (cytomegalovirus, Epstein-Barr virus, varicella-zoster, herpes simplex) can cause ALF. Herpes simplex virus 1 and 2 (HSV) are the predominant cause of viral-induced ALF during the first month of life. Babies present with fever, rash, lethargy, poor feeding, and raised transaminases (in thousands). Treatment with high-dose acyclovir should be initiated in all neonates with ALF, until the results for HSV are known. Dengue virus causing ALF has been reported in tropical countries.

Drugs and toxins

Drug-induced hepatoxicity can be a dose-dependent response, an idiosyncratic reaction, or a synergistic reaction. Some indigenous or herbal medicines are also hepatotoxic. Acetaminophen is the most common drug associated with ALF. Genetic polymorphism of cytochrome P450 isoenzymes predisposes to acetaminophen toxicity due to increased toxic intermediates production. Anti-tuberculosis drugs, particularly isoniazid, are associated with ALF. The mechanism of toxicity is similar to acetaminophen, oxidation via cytochrome P450 pathway resulting in toxic metabolites.

The true incidence of idiosyncratic drug-induced liver injury (DILI) is unknown, maybe up to 14 new cases/100 000/year. Antibiotics and NSAIDs are the most common causes. Around 8% of DILI develop ALF. Genetic susceptibility to certain drugs and underlying mitochondrial cytopathies are proposed causes. Councils for International Organizations of Medical Sciences/Roussel-Uclaf Causality Assessment Method (CIOMS/RUCAM) scales are helpful in establishing causal relationship between a drug and liver damage. Using the scoring system, suspected drugs could be categorized into ''definite or highly probable'', ''probable'', ''possible'', ''unlikely'' and ''excluded''. Chemotherapy drugs are known to induce veno-occlusive disease leading on to ALF.