Acute liver failure in neonates

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Abstract  Acute liver failure (ALF) in neonates is a rare but often fatal event. Though in adults and older children, a main symptom of ALF is hepatic encephalopathy, this is very difficult to diagnose and prove in infants. Causes of ALF in neonates encompass metabolic, infectious and haematological disorders, congenital vascular/heart abnormalities, and drugs. Infants with ALF should only be treated in specialised paediatric hepatology centres with facilities for liver transplantation, since for many liver transplant, with a long term survival of over 60%, is the only therapeutic option.

KEYWORDS
Neonatal acute liver failure; Coagulopathy; Herpes simplex virus; Metabolic disease; Neonatal haemochromatosis; Liver transplant

1. Definition

The definition of ALF in children and neonates is a subject of controversy. In adults, in 1970, Trey and Davidson defined ALF as “a potentially reversible condition, the consequence of severe liver injury, in which the onset of hepatic encephalopathy is within eight weeks of the first symptoms of illness, in the absence of pre-existing liver disease” [1]. This definition is unsatisfactory for children, especially during infancy, not only because it is very difficult to identify signs of encephalopathy in this age group, but also because encephalopathy can be a very late event in the course of the disease. Moreover, children presenting with ALF often do have an underlying unrecognized liver disease. Bhaduri and Mieli-Vergani have addressed this issue and proposed the following definition of ALF in children: “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 recognised underlying chronic liver disease” [2].

1.1. Aetiology

Causes of ALF during the newborn period are listed in Table 1 [3,4] and include inborn errors of metabolism, perinatal infections, hypotension/shock, and haematological conditions like haemophagocytic lymphohistiocytosis. Identifying the cause of ALF not only provides indication of prognosis but also dictates specific management options.

1.2. Viral infections

Perinatal infection with viruses of the herpes family, adenovirus, parvovirus and hepatitis B can cause ALF in newborn babies [5,6]. Herpes simplex virus (HSV) induced ALF is the most common among viral aetiologies, carries a high mortality and is rarely accompanied by skin lesions, hence it should be considered in all sick babies with coagulopathy and raised transaminases. Infants with this presentation should be promptly started on intravenous aciclovir. We have analysed retrospectively the case notes of 11 patients with HSV induced ALF. A history of possible herpes infection was elicited in 5 parents, but HSV had not been suspected clinically. All patients were asymptomatic when discharged from postnatal units, and presented with non-specific symptoms of poor feeding and lethargy within 2 weeks from birth. All had grossly deranged liver function and coagulopathy at presentation. Seven of the 11 patients had HSV-1 infection, 4 HSV-2. Only two patients, both of whom received early treatment with intravenous aciclovir survived. These findings indicate that it is important to recognise HSV infection in women of childbearing age and their sexual partners and to treat the infected baby as soon as possible.

1.3. Metabolic diseases

Inherited disorders of metabolism are an important cause of ALF in the neonatal period, and must be promptly investigated because dietary manipulation or disease specific treatment may be life saving. The most common metabolic diseases to be considered are galactosaemia, hereditary fructose intolerance, and tyrosinaemia [3–9]. For the first two, withdrawal of the offending dietary component is usually life saving. The management of tyrosinaemia has changed dramatically since the introduction of 2(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexenedione (NTBC), which prevents the formation of toxic metabolites and produces rapid clinical and biochemical improvement [7]. Recently, mitochondrial respiratory chain defects have been implicated as an etiological factor for ALF in infants. They usually present with hypoglycemia, vomiting, coagulopathy, acidosis and raised lactate with or without neurological symptoms [10]. Rarely fatty acid oxidation defects and inborn errors of bile acid synthesis present with ALF. Neonatal haemochromatosis (NH) is usually listed under the metabolic disorders associated with ALF in infancy, though its aetiopathogenesis is unknown. It is a rare disease, but the most common cause of ALF in the neonatal period. In NH, liver injury of fetal onset is associated with massive intra and extra hepatic iron deposition sparing the reticulo-endothelial system. It presents with acute liver failure around birth. It has been suggested that it may be the ultimate phenotype of different aetiologies. There is an 80% recurrence rate within families of affected children. The description of NH in half siblings born to the same mother has led to

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Diagnostic test</th>
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<tr>
<td>Galactosemia</td>
<td>Red cell galactose-1-phosphate uridyl transferase</td>
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<td>Tyrosinemia</td>
<td>Urine succinyl acetone</td>
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<td>Neonatal haemochromatosis</td>
<td>Raised ferritin, extrahepatic iron deposition</td>
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<td>Haemophagocytic lymphohistiocytosis and congenital leukaemia</td>
<td>Bone marrow examination</td>
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<td>Septicemia and shock</td>
<td>Positive cultures, clinical scenario</td>
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<td>Giant cell hepatitis with hemolytic anemia</td>
<td>Coombs positive haemolytic anemia</td>
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<tr>
<td>HHV-6, Hepatitis B, Adenovirus, Parvovirus</td>
<td>Viral serology and PCR</td>
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<td>Mitochondrial hepatopathy</td>
<td>Mitochondrial DNA, muscle and liver biopsy (open, if coagulopathy permits) for quantitative respiratory chain enzyme determination</td>
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<td>Vascular malformations and congenital heart disease</td>
<td>Echocardiography</td>
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<td>Maternal overdose (paracetamol) [3]</td>
<td>History and drug levels</td>
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<td>Hypocortisolism [4]</td>
<td>Cortisol levels, short synacthen test</td>
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the suggestion that the disease could be due to incomplete penetrance or gonadal mosaicism for a dominant disorder or a mitochondrial defect, rather than be autosomal recessive, but the precise pattern of inheritance is unknown. Other proposed causes of NH are intrauterine infection and maternal alloimmune antibodies. There is often a history of maternal anaemia, oligohydramnios or megalaplaenta. There are no specific diagnostic tests for NH, but hypersaturation of transferrin with elevated ferritin levels are useful biochemical clues in a baby with ALF. The diagnosis can only be confirmed by the demonstration of extra hepatic iron deposits sparing the reticuloendothelial system, which in vivo can be sought by performing a biopsy of lip salivary glands. Intra-hepatic iron deposition on its own is not diagnostic, because the neonatal liver is physiologically iron overloaded and high hepatic iron content is observed in any form of severe liver disease in this age group. Magnetic resonance imaging of the abdomen may demonstrate iron storage in the pancreas, but iron storage is typically absent in the spleen. The prognosis of NH has been universally reported as poor. Chelation treatment alone is ineffective in altering the course of the disease. Specific management includes the use of an antioxidant cocktail [11,12] (Table 2), but its efficacy has not been tested in controlled trials and in our own series of 19 patients it has not modified the outcome [11]. Liver transplantation is the only therapeutic option for severely affected babies and is performed successfully even during the first few days of life, though the waiting period for a suitable size donor is usually long, given the small size of the recipient. While waiting for transplantation, single volume whole blood exchange transfusion may be helpful to manage symptomatic coagulopathy, and possibly to remove maternal alloantibodies that have been recently suggested to play a significant role in the pathogenesis of this condition. The survival after liver transplantation for NH in our center is 50% (median follow up 7.8 years, range 3–10 years) [11]. Antenatal administration of intra-venous immunoglobulins weekly from the 18 week of gestation until term has been shown to reduce the severity of the illness in the newborn in a series of 15 pregnant mothers who previously had an affected baby [13].

1.4. Ischemic injury

Shock liver can occur after cardiac arrest, a period of hypotension/hypovolaemia or in the setting of congestive cardiac failure, even when hypotension is not clearly documented. Serum transaminase levels are markedly elevated but they do normalize rapidly once the circulatory problem is stabilized [5].

1.5. Vascular causes

Congestive heart failure of any aetiology can present as liver failure. Conditions that we have seen in our unit presenting as ALF include hypoplastic left heart, coarctation of the aorta and right heart failure. Ascites, significant hepatomegaly, coagulopathy and hypoalbuminemia are often present [5].

1.6. Hematological malignancies

Haemophagocytic lymphohistiocytosis (HLH) presents with fever, hepatosplenuemgaly, pancytopenia and, in severe cases, with ALF. Biochemically, there are high serum triglycerides and low fibrinogen. Usually, these patients bleed severely from venepuncture sites, in contrast to infants with other forms of ALF. Bone marrow aspiration or cytospin from body fluids (ascites, cerebrospinal fluid) usually demonstrate haemophagocytosis. When HLH presents with ALF, mortality is high despite aggressive supportive treatment, chemotherapy and bone marrow transplantation [14]. Haematologic malignancies, e.g., congenital leukemia, can present with ALF due to massive infiltration of the liver. The presence of high fever with hepatosplenuemgaly, high alkaline phosphatase, high lactate dehydrogenase and abnormalities of the peripheral blood film suggest the diagnosis and bone marrow examination confirms it [15,16].

2. Management

2.1. General measures

Patients with ALF should be nursed in a quiet environment with as little stimulation as possible to minimize acute increases in intra-cranial pressure.

<table>
<thead>
<tr>
<th>Table 2 Anti oxidant cocktail for neonatal haemochromatosis</th>
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<tr>
<td>Vitamin E</td>
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<tr>
<td>N-acetylcysteine</td>
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<td>Prostaglandin–E1</td>
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<td>Selenium</td>
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<td>Desferoxamine</td>
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Babies with encephalopathy and those without encephalopathy, but an international normalized prothrombin ratio (INR) greater than 4 should be admitted to the intensive care unit for continuous monitoring. Patients should be carefully monitored in respect of haemodynamics and fluid management (blood pressure, urine output), metabolic parameters (electrolytes, blood sugar) and neurological status (presence of encephalopathy). Sedation should be avoided unless the patient is to be mechanically ventilated, as it can interfere with the monitoring of the neurological status. Coagulation and metabolic parameters, full blood count and arterial blood gases in ventilated patients should be regularly checked. Controlled trials in adults have failed to substantiate any beneficial effect of corticosteroids, interferon, insulin and glucose, prostaglandin E1, bowel decontamination, and charcoal hemoperfusion in patients with ALF. Maintenance of nutrition is crucial and hypoglycemia should be avoided by use of intravenous glucose infusion or by ensuring adequate enteral intake. Total fluid intake is restricted to two-thirds of the maintenance if the patient is not dehydrated. The concept of protein intake aggravating or precipitating hepatic encephalopathy has now been discarded, and adequate calories should be provided using oral or nasogastric feeding. Investigations to elucidate the cause of ALF should be performed urgently to start appropriate treatment. Liver biopsy is only rarely useful and usually contraindicated because of severe coagulopathy.

3. Complications

3.1. Encephalopathy

The most serious complications of ALF are cerebral oedema with resultant intracranial hypertension and hepatic encephalopathy. Encephalopathy usually presents late in the course of the illness, and when present carries a bad prognosis. The conventional grading system for encephalopathy (grade I–IV) used for adults and older children is not applicable to babies. Signs of early encephalopathy in babies are inconsolable crying and sleep disturbance, which can progress to somnolence or irritability and later to frank coma more or less responsive to painful stimuli. The infant should be electively ventilated and sedated at the first signs of encephalopathy. Mannitol, an osmotic diuretic that remains the mainstay of treatment for increased ICP in adults and older children, is not often used in babies, for whom we prefer using exchange transfusions.

3.2. Infection

Patients with ALF have impaired immune function. About 60% of deaths in ALF have been attributed to sepsis. An active uncontrolled infection is also a relative contraindication for liver transplantation. The risk factors for infections include coexisting renal failure, cholestasis and treatment with thiopental. In adults, the presence of encephalopathy (grade II or above) has been shown to be associated with bacterial infection in about 80% of cases and fungal infections in about 32% of cases. The most common bacterial infection is due to *Staphylococcus aureus*, but streptococci or gram negative organisms such as coliforms are also isolated. Prophylactic intravenous antibiotics have been shown to reduce the incidence of culture-positive bacterial infection from 61.3% to 32.1% in adult patients. *Candida* species are the most common fungal isolates which are often unrecognized and may be ominous. Deterioration of encephalopathy after an initial improvement, a markedly raised leukocyte count, pyrexia unresponsive to antibiotics, and established renal failure are strong indicators of fungal infection [17,18]. In our unit, neonates with ALF are treated from admission with broad spectrum antibiotics (usually third generation cephalosporin and an aminoglycoside), acyclovir and fluconazole.

3.3. Coagulopathy

The prothrombin time, expressed as INR, is used as an indicator of the severity of liver damage and to decide when to list for transplantation. An INR ≥ 4 is associated with more than 90% mortality and is the main parameter used in our centre for transplant listing. Thus, correction of coagulopathy is indicated only if the patient is already listed for transplant or prior to invasive procedures. Significant disseminated intravascular coagulation is unusual in ALF. The risk of hemorrhage does not correlate with INR but with thrombocytopenia which can develop rapidly. A platelet count of less than $10^9/L$ has been reported in about two-thirds of adults with ALF. Common sites of internal haemorrhage include the gastrointestinal tract, nasopharynx, lungs, and retroperitoneum. Intracranial hemorrhage is uncommon. The presence of significant disseminated intravascular coagulation usually indicates sepsis or secondary HLH. Prophylactic ranitidine or proton
pump inhibitors have been shown to decrease the incidence of gastric bleeding [19].

3.4. Haemodynamic complication

The early haemodynamic changes in ALF patients are similar to those seen in the systemic inflammatory response syndrome and reflect a state of hyperdynamic circulation with decreased systemic peripheral vascular resistance and increased cardiac output. Circulatory failure is a common mode of death in patients with ALF, often complicating sepsis or multiorgan failure. Invasive haemodynamic monitoring like arterial blood pressure, central venous pressure or lately use of PICCO and oesophageal echocardiography in adults may provide early evidence of circulatory failure and is helpful in deciding fluid management, but may be difficult in small infants. In the presence of persistent hypotension despite normal filling, noradrenaline is the inotropic agent of choice. N-acetylcysteine has been shown to improve parameters of oxygen metabolism. A combination of prostacycline and N-acetylcysteine has been found to be more beneficial for oxygen metabolism than either drug alone [20,21].

3.5. Renal failure

Renal failure with severe oliguria often develops in ALF, especially in later stages. In the pediatric population, the incidence of renal failure is lower (10—15%) than in the adult population (30%) but there are no studies in neonates [21]. Renal failure could be due either to a direct toxic effect on the kidneys, as in paracetamol overdose, or to a complex mechanism such as hepatorenal syndrome or acute tubular necrosis secondary to complications of ALF (sepsis, bleeding, and/or hypotension). Although the mechanism of renal failure is not clear, it is essential to correct intravascular hypovolemia. Continuous filtration or dialysis systems are associated with less haemodynamic instability and consequently less risk of aggravating latent or established encephalopathy than intermittent haemodialysis.

3.6. Metabolic derangement

Hypoglycaemia is present in some 40% of patients with ALF. The classic signs and symptoms of hypoglycemia are often masked, especially in the presence of encephalopathy, hence regular blood glucose monitoring is mandatory as hypoglycemia can worsen the encephalopathy and cause rapid neurologic deterioration. Acid—base imbalance is common. Metabolic acidosis is present in about 5% of patients with ALF and is associated with poor outcome. Lactic acidosis is related to inadequate tissue perfusion. Sometimes respiratory alkalosis or acidosis may complicate the clinical picture.

3.7. Liver transplantation

Advances in surgical techniques have made it possible to perform liver transplantation in newborn babies. The availability of liver transplantation for this age group has significantly improved survival, but the procedure is contraindicated in patients with advanced complications of ALF, such as fixed and dilated pupils, uncontrolled sepsis, and severe respiratory failure (adult respiratory distress syndrome) or conditions not treatable by liver replacement, such as mitochondrial cytopathies with neurological involvement, HLH, giant cell hepatitis with Coombs positive haemolytic anaemia (which recurs after transplant) and malignancies. Though worse than for older children, the outcome of neonatal liver transplantation is acceptable, with a patient survival of about 65% in our centre, the downside being a life long need for immunosuppressive medications [22,23].

4. Hepatocyte transplantation

Liver cells isolated from unused donor livers can be infused in to the failing liver to provide a functioning hepatic mass while the native liver regenerates. The procedure has shown some encouraging results as a bridge to transplant, however, the technique remains experimental [24].

5. Liver support systems

In ALF, there is impairment of synthetic, detoxifying, and biotransformatory activity resulting from the loss of functioning hepatocytes and Kupffer cells. Theoretically a support device, which provides all these functions would be ideal, either as a bridge to liver transplant or, better, to obviate the need for it, by supporting liver function while the native liver regenerates. Liver support devices could be either cleansing devices or bioartificial liver support systems. Cleansing devices perform only the detoxifying function of the liver, whereas bioartificial liver support systems have the theoretical advantage of having synthetic and detoxi-
fying properties. None of these devices have been tried systematically in children or neonates hence their use outside research protocols is not recommended [25—27].

6. Conclusions

ALF is a multisystem disorder with a high mortality rate, which should be managed in a specialized paediatric liver centre with facilities for liver transplantation, since this procedure, despite improvement in intensive care support, remains the only effective mode of treatment for most infants. Liver assist devices and hepatocyte transplant hold a great potential of providing a bridge to transplant or avoiding it while the native liver regenerates, but are still at the experimental stage.

References