Acute fatty liver of pregnancy: A report of two cases

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ABSTRACT
Acute fatty liver of pregnancy is an uncommon, potentially fatal disorder. Between 1998 and 2000, two patients with acute fatty liver of pregnancy presented at the Christian Medical College Hospital, Vellore. Both patients were in the thirty-sixth week of pregnancy. Jaundice and encephalopathy were the predominant symptoms. Both the mothers died after they delivered a stillborn infant each. The maternal deaths were due to multorgan failure and/or postpartum haemorrhage and sepsis. The route of delivery was vaginal in both the patients. Extrahepatic and metabolic complications in both cases included renal failure, sepsis, hypoglycaemia, disseminated intravascular coagulation and gastrointestinal bleeding. Liver biopsy done in both patients was consistent with the diagnosis of acute fatty liver of pregnancy. To the best of our knowledge, this is the first report from India on acute fatty liver of pregnancy.

INTRODUCTION
Acute fatty liver of pregnancy (AFLP) is an uncommon, completely reversible, yet potentially fatal disorder. It occurs in the third trimester of pregnancy and has well-defined clinical, laboratory and histopathological features, which are not pathognomonic. An early diagnosis, rapid delivery of the foetus, availability of trained personnel and intensive care facilities have been shown to result in improved maternal and foetal survival. We report our experience of two patients with AFLP, the first such report from India on acute fatty liver of pregnancy.

THE CASES
Between 1998 and 2000, 23 pregnant women with acute hepatic dysfunction presented at the Christian Medical College Hospital, Vellore. Of these, 18 patients satisfied the standard criteria for the diagnosis of AFLP (see Box). However, consent to perform a liver biopsy was obtained in only 4 patients. Two of these 4 biopsies were obtained post mortem and were consistent with the diagnosis of AFLP.

Patient 1 was a 21-year-old second gravida, who had onset of symptoms in the thirty-sixth week of pregnancy with jaundice and encephalopathy. She did not have predominant cholestatic symptoms or polydipsia. She had undergone a vaginal delivery 6 days after the onset of symptoms and had delivered a stillborn girl child. Following the delivery, she was referred to our hospital.

Patient 2 was a 17-year-old first gravida, who also had onset of symptoms in the thirty-sixth week of pregnancy and was referred to our hospital. A vaginal delivery was conducted on day 5 after the onset of symptoms. Her predominant symptoms also were jaundice and encephalopathy and she had ascites at the time of presentation to our hospital. A history of consanguinity was present. The outcome of the delivery was a stillborn girl child. Both mothers died 2–4 days after delivery.

The following tests were done on both the patients at admission and serially when required: haemoglobin, total white cell count, differential count, blood picture, work-up for disseminated intravascular coagulation (DIC), platelet count, liver function tests, serum creatinine, lactate dehydrogenase, serum electrolytes, serum caeruloplasmin, serum copper, antinuclear antibody, blood sugar, uric acid, serum amylase and routine analysis of urine.

Hepatitis B surface antigen (HBsAg), HIV, VDRL, IgM hepatitis A virus, IgM hepatitis E virus, and hepatitis C virus (third-generation EIA) antibodies were tested in both patients and were found negative. Both patients were managed in the intensive care facility.

Fresh frozen plasma, platelet-rich concentrate and packed cell transfusions were given to maintain an international normalized ratio (INR) of <1.5, platelets of >50x10^9/L and a haemoglobin of >8 g/dl, respectively. Antibiotics (ampicillin, ciprofloxacin and metronidazole) were started before delivery and the patients received 10% dextrose infusion. On documentation of hypoglycaemia, 50% dextrose boluses were added till normalization of blood sugar.

Table I gives the laboratory findings. Both patients had direct hyperbilirubinaemia with serum bilirubin values of >15 mg/dl. The serum albumin was low and the aspartate aminotransferase,
Table I. Laboratory findings

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>15.9</td>
<td>38.0</td>
</tr>
<tr>
<td>Total</td>
<td>15.9</td>
<td>38.0</td>
</tr>
<tr>
<td>Direct</td>
<td>10.7</td>
<td>28.0</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>270</td>
<td>280</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>275</td>
<td>180</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>558</td>
<td>1332</td>
</tr>
<tr>
<td>Random blood sugar (mg/dl)*</td>
<td>106</td>
<td>45</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>3.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Prothrombin time in seconds (patient/control)*</td>
<td>60/10</td>
<td>60/11</td>
</tr>
<tr>
<td>Platelet count (cmm)*</td>
<td>126 000</td>
<td>69 000</td>
</tr>
</tbody>
</table>

*worst values within 72 hours of delivery. All other values at admission

Normal values: total bilirubin: 0.2–1 mg/dl, direct bilirubin: 0.2–0.5 mg/dl; serum albumin: 3.7–4.9 g/dl; alanine aminotransferase: <40 U/L; aspartate aminotransferase: <40 U/L; alkaline phosphatase: 40–125 U/L; serum creatinine: 0.5–1.4 mg/dl

alanine aminotransferase and alkaline phosphatase were elevated. A high uric acid level was seen in the second patient. Neither patient had albuminuria. At admission, the prothrombin time was prolonged and platelets were low (<150 000/cmm) in both patients.

Abdominal ultrasound showed a fatty liver and ascites in both patients. Splenomegaly and biliary obstruction were absent in both patients.

Hospital course

Leucocytosis was present in both patients. Patient 1 had culture-negative neutrocytic ascites. Patient 2 required a therapeutic paracentesis. Patient 1 had schistocytes and Burr cells, and deranged coagulation parameters strongly suggestive of DIC. Patient 2 had bleeding from venepuncture sites, schistocytes on peripheral smear, prolonged coagulation parameters but a negative paracoagulation test. She received cryoprecipitate transfusion. Both patients had elevated creatinine levels. Hypoglycaemia was seen in Patient 2. Both required ventilatory support. Patient 1 developed gastrointestinal bleeding due to reflux oesophagitis. Patient 2 had atomic postpartum haemorrhage. Patient 1 developed renal failure, gross ascites, right-sided pleural effusion, spontaneous bacterial peritonitis, DIC and severe metabolic acidosis. She died on the fourth day after delivery. Patient 2 had atomic postpartum haemorrhage, DIC, renal failure and severe metabolic acidosis. She died on the second day. We received the patients in multiorgan dysfunction with severe metabolic acidosis. Probably the late presentation after the onset of illness resulted in death.

Histopathological findings of liver biopsies

The liver biopsy was obtained in both these patients post mortem. The biopsies showed diffusely swollen hepatocytes with microvesicular fatty change (Fig. 1), which was more prominent in the perivenular region, extramedullary haemopoiesis, mild lobular and portal inflammation, ceroid-laden Kupffer cells and macrophages and, in one patient, diffuse canicular and mild hepatocytic cholestasis. Bile ductular proliferation was present in one biopsy. The histological features were in keeping with AFLP.

DISCUSSION

Acute fatty liver of pregnancy is classified under acute hepatic failure—not otherwise classified. Its incidence ranges from 1 in 7000 to 1 in 15 000 deliveries. AFLP has been reported to be more common in multiple gestations and with male foetuses. Jaundice and encephalopathy are the common presenting symptoms. The absence of jaundice and occurrence of polydipsia and pruritus have been reported; however, these symptoms were not seen in our patients.

A low albumin, a greater than 5-fold elevation of alkaline phosphatase and a moderate elevation of transaminases have been reported. A prolonged prothrombin time, essential to the diagnosis of AFLP, was seen in both patients. An elevated creatinine value, which is seen in the majority of patients with AFLP and is to be considered as 'forme fruste' of AFLP, was found in both patients. Portal hypertension and spontaneous bacterial peritonitis have been documented in this disorder. One of our patients developed culture-negative neutrocytic ascites and one had gastrointestinal bleeding. The causes of gastrointestinal bleeding described in various reports include oesophageal variceal bleed in addition to Mallory–Weiss syndrome, acute gastric or duodenal lesions and as a manifestation of coagulopathy.

Disseminated intravascular coagulation was seen in both patients as well as hypoglycaemia, which is a common manifestation as reported in other studies.

Fatty liver on ultrasound was seen in both our patients. The usefulness of various imaging modalities in the diagnosis and management of AFLP has been described. The standard criteria for the diagnosis of AFLP, the indications for liver biopsy and the histopathological findings on liver biopsy have been well documented.

The differential diagnosis in a patient who presents with features of AFLP includes acute viral hepatitis and pre-eclampsia. The difficulty in differentiating AFLP from acute viral hepatitis and the differentiating features between AFLP and HELLP (Haemolysis, Elevated Liver enzymes, Low Platelets) syndrome have also been described.

Early recognition, early termination of pregnancy, availability of well-equipped intensive medical care units, provision of aggressive supportive care of liver failure and management of complications of liver failure have resulted in 100% maternal survival as compared to the high maternal mortality and morbidity reported earlier. The causes of foetal mortality include pre-term delivery and maternal DIC. The rationale of early delivery based on good clinical judge-
ment seems to be supported by the finding that no patient has yet recovered from AFLP before delivery. The route of delivery in patients with AFLP is controversial. The advantages and disadvantages of a caesarean section and vaginal delivery have been addressed. We advocate that labour should be induced if AFLP is one of the differential diagnoses in the patient. AFLP and pre-eclampsia present with a poorly defined overlap of clinical symptoms and signs and recurrence of AFLP has been reported. The pathogenesis of AFLP is not clear. A defect in the intramitochondrial beta-oxidation of fatty acids has been found to be responsible for the manifestations of AFLP. Vomiting, coma and hyperammonaemia are common to all mitochondrial hepatopathies. Children with defects in the early stages of the intramitochondrial pathway present with severe energy deficiency and die before 2 years of life, while those with defects in the later stages present with symptoms of failure to thrive.

Long chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) deficiency has been demonstrated in skin fibroblast culture in patients diagnosed to have AFLP. LCHAD deficiency has been identified to be due to mutations at G1528C. AFLP is manifest when the foetus is homozygous for the defect in a mother who is heterozygous for the defect. Mothers who carry heterozygous foetuses do not develop the disease. Consanguinity was seen in one of our patients. Genetic studies will help identify specific mutations in our population and are useful for the prenatal diagnosis of foetal homozygosity for LCHAD deficiency. Such studies are also useful in diagnosing the disease and for offering appropriate dietary advice for newborns.

The absence of recurrence of AFLP in every pregnancy, absence of geographic or ethnic clustering and familial accumulation do not support a genetic cause. The identification of the defect in a mother with a prenatal diagnosis of homozygosity of the foetus will help reduce complications and ensure improved maternal survival.

The major clinical manifestation of inherited mitochondrial disorders of FAO include hepatic steatosis, elevated aminotransferase levels, coagulopathy, hyperammonaemia, hypoglycaemia and hypoketosis, cardiomyopathy, congestive heart failure, cardiac arrhythmia, sudden infant death, rhabdomyolysis, vomiting, lethargy, coma, encephalopathy, increased lactate and uric acid, myoglobinuria, renal tubular acidosis, failure to thrive and pancreatitis. AFLP has not been reported from the Indian subcontinent and, to the best of our knowledge, this is the first report of two patients.

ACKNOWLEDGEMENT

We thank Professor Robert G. Batey, Director and Head, Department of Gastroenterology, John Hunter Hospital, New South Wales, Australia for reviewing the manuscript and for offering valuable suggestions and advice.

REFERENCES