

*Leading article*

## Acute fatty liver of pregnancy and the microvesicular fat diseases

Acute fatty liver of pregnancy was probably first described by Farnier in 1857<sup>1</sup> and the first case report, in 1934, was by Stander and Cadden.<sup>2</sup> The first full description of the disease is usually attributed to Sheehan<sup>3</sup> who, in 1940, described obstetric yellow atrophy as a specific cause of jaundice of pregnancy. He distinguished it histologically from acute yellow atrophy (fulminant hepatitis) by the absence of liver necrosis in the presence of microvesicular fat, with swollen hepatocytes with central nuclei and periportal sparing. Only about 100 patients have been reported in the English literature, mainly as single case reports, the largest being Sheehan's two series<sup>3 4</sup> of 15 patients, but there was scanty clinical detail concerning individuals. The largest with full details is the report by Burroughs and coworkers<sup>5</sup> of 12 patients with idiopathic acute fatty liver of pregnancy seen at the Royal Free Hospital between 1968 and 1980. The condition is therefore rare.

The onset of acute fatty liver of pregnancy is between the 30th and 38th week of pregnancy, marked by nausea, repeated vomiting, and abdominal pain, followed about a week later by jaundice. In some patients preceding hypertension, peripheral oedema, and proteinuria suggest pre-eclampsia. The condition is more common with twin and male births and in primipara.<sup>5</sup> In the severely affected the course is marked by coma, renal failure, and haemorrhages. The infant is usually stillborn, or labour is induced. High serum uric acid levels are usual and these may be related to tissue destruction and lactic acidosis. This is not a usual feature of viral hepatitis or acute liver failure, but is found in toxæmia of pregnancy. Hyperbilirubinaemia is found without demonstrable haemolysis, and this is in contrast with pre-eclampsia or eclampsia, where jaundice is rare except with haemolysis. The aspartate transaminase values are raised, but gamma globulin concentrations are normal. Blood films show a characteristic picture of neutrophilia, thrombocytopenia, normoblasts, giant platelets, and basophilic stippling. This combination of features is not seen in pre-eclampsia or viral hepatitis and provides a strong pointer towards the diagnosis of acute fatty liver of pregnancy.<sup>5</sup> Disseminated intravascular coagulation of varying severity may be a complication.

Formerly the maternal mortality of acute fatty liver of pregnancy was believed to be very high – about 75–85% – and the fetal mortality about 85%.<sup>7 8</sup> More recent figures, however, are much more satisfactory and of 12 patients seen at the Royal Free Hospital, only four mothers died (33.3%) and the fetal mortality was 66.7%.<sup>5</sup> This improvement can be attributed to early caesarean section and induction of labour and to diagnosis of the less severe cases. Death is usually because of extrahepatic causes such as disseminated intravascular coagulation with massive

haemorrhage and renal failure, which do not occur in the less severely affected.<sup>9</sup> The non-fatal form of the disease is well described by Bernuau and colleagues from Paris.<sup>10</sup> None of their four patients developed coma and the course was remarkably benign. Failure to recognise milder acute fatty liver results from not considering the diagnosis more often in any patient during the last trimester of pregnancy who becomes nauseated and vomits repeatedly. There is also reluctance to perform liver biopsy in a pregnant woman with impaired clotting. This can be achieved, however, using the transvenous (transjugular) approach.<sup>10 11</sup> Later, liver biopsy may not seem to be justified because the patient seems to have recovered. Finally, the liver specimen may have been taken too late when the histological lesions have already disappeared. Cytoplasmic fat-filled microvacuoles may be clearly recognised only on frozen sections stained for fat with such methods as oil-red O.<sup>10</sup> CT scanning may be a useful, non-invasive alternative to liver biopsy, as low attenuation ratios indicate fat accumulation in the liver.<sup>12</sup>

The prognosis for subsequent pregnancies is good for those mothers who recover, and in the Royal Free Hospital series four patients had seven subsequent normal pregnancies.<sup>5</sup>

Acute fatty liver of pregnancy must be considered a member of the microvesicular fat disease group (Table). This includes Reye's syndrome, vomiting disease of Jamaica, sodium valproate hepatotoxicity, tetracycline toxicity (with which acute fatty liver of pregnancy has been associated<sup>13</sup>), and congenital defects of the urea cycle enzymes. They all show the same general pattern. The onset is marked by fatigue, nausea, vomiting, often severe and persistent, with variable jaundice, impairment of consciousness and coma. Also fits may occur. Renal failure and disseminated intravascular coagulation of varying severity may be complications. The liver is not the only organ involved, and triglyceride accumulations may be found in the renal tubules and occasionally in myocardium and pancreas. Liver failure does not seem to be the usual cause of death. Coma may be related to increases in blood ammonia levels, or to cerebral oedema. Bleeding is because of disseminated intravascular coagulation, rather than to failure of the liver to synthesise clotting factors.

Hepatic histology shows centrilobular microvesicular fat. Cell necrosis is variable and minor, although occasionally there may be massive centrilobular necrosis. The hepatocytes show central nuclei with prominent nucleoli. The inflammatory reaction is minimal and centrilobular cholestasis is occasionally found. Frozen sections stained for fat are necessary for

Table *Microvesicular fat diseases*

Acute fatty liver of pregnancy	Sodium valproate toxicity
Reye's syndrome	Congenital defects of urea cycle enzymes
Vomiting disease of Jamaica	
<i>Features</i>	
Vomiting	Hypoglycaemia
Variable jaundice	Rise serum fatty acids
Coma	Liver biopsy – microvesicular fat
Disseminated intravascular coagulation	– necrosis and cellular infiltration
Renal failure	not prominent
Rise blood ammonia levels	Electron microscopy – mitochondrial abnormalities

diagnosis in mild cases. Electron microscopy shows that the mitochondria are swollen, pleomorphic and varying in shape.<sup>5 14 15</sup> The ribosomal pattern in the rough endoplasmic reticulum is also abnormal.

The diseases can be related to a widespread hepatic metabolic disturbance, particularly involving mitochondria and ribosomes.<sup>16</sup> Blood ammonia levels are raised, and citrulline values low. This can be related to reduction of hepatic mitochondrial Krebs cycle enzymes which have been shown to be reduced in both fatty liver of pregnancy<sup>15</sup> and Reye's syndrome.<sup>17</sup> The amino acid profile shows high glutamine, alanine, and lysine levels in both fatty liver of pregnancy<sup>5</sup> and in Reye's syndrome.<sup>18</sup>

Hypoglycaemia is frequent, and has been described in acute fatty liver of pregnancy,<sup>19</sup> in Reye's syndrome,<sup>20</sup> in the vomiting disease of Jamaica,<sup>21</sup> and with sodium valproate hepatotoxicity.<sup>22</sup> The citric acid cycle enzymes also reside in the mitochondria and inhibition of this glycolytic system may contribute to the low blood glucose.<sup>23</sup> Hypoglycaemia may also reflect fall in ribosomal glucose 6-phosphatase function.

The accumulation of triglycerides within hepatocytes is the hallmark of this group of diseases. It reflects interference with the exit of lipid from the liver through depression of synthesis of the apoprotein of very low density lipoproteins. Mitochondrial injury would also depress oxidation of fatty acids. A block in the beta oxidation of fatty acids has indeed been shown in the liver of patients with Reye's syndrome.<sup>24</sup> Plasma free fatty acids are increased in Reye's syndrome; the activated form of the long chain fatty acids in the liver, the coenzyme A (co A) esters, exert inhibitory effects on mitochondrial function.<sup>25</sup>

Young people are predominantly affected in Reye's disease, the vomiting disease of Jamaica, and in congenital defects of urea cycle enzymes. Patients with acute fatty liver of pregnancy are usually reasonably young. Adverse hepatic effects of sodium valproate are roughly twice as frequent in children than in adults.<sup>26</sup> This seems to be the only drug-related liver injury to affect children. This has led to the hypothesis that all these diseases primarily affect patients having an underlying defect in fatty acid metabolising enzymes.<sup>27</sup>

The mode of initiation of these microvesicular fat diseases is diverse and in most instances not fully understood. Viral, toxic, and nutritional factors have been implicated. Virus infections have been particularly associated with Reye's syndrome where an acute respiratory infection often precedes the acute episode. This has also been described for acute fatty liver of pregnancy.<sup>28</sup> In the case of Reye's syndrome, at least 19 different viral agents, influenza B and varicella being the most frequent, may cause the prodromal illness. The viral-host interaction is said to be modified by some exogenous agent. In the case of Reye's syndrome, this may be salicylates given to the child with a respiratory infection.<sup>29</sup> In one study 97% of 98 children with Reye's syndrome had taken aspirin in the week before admission, compared with 71% of controls. Insecticides have also been incriminated in Reye's syndrome and it has been suggested that those carrying insecticides in their fatty tissue may have an enhanced response to a virus.<sup>30</sup> Aflatoxin has also been suggested as the synergistic toxin, but there is little evidence to support this view.<sup>31</sup> Large doses of intravenous tetracycline, a known inhibitor of protein synthesis, have been associated with acute fatty liver of pregnancy.<sup>13</sup> In vomiting disease of Jamaica, the

injurious agent is hypoglycin A derived from Ackee apples, which is converted to a toxic metabolite.<sup>21</sup>

Perhaps the most exciting mechanism is that postulated for sodium valproate hepatotoxicity.<sup>22</sup> The reaction to this anticonvulsant usually develops within six months of starting the drug. The microvacuolar steatosis is said to be caused by oxidation of the valproate, with ensuing production of toxic metabolites that are structurally related to the hepatotoxic 4-pentenoic acid<sup>32</sup> and to the metabolites of hypoglycin A that have been incriminated in Jamaican vomiting sickness.<sup>21</sup>

Nutritional factors are even less clearly defined, although any agent injurious to the hepatocyte would be expected to be more harmful in the protein depleted. Similar hepatic lesions are seen in experimental animals given substances such as ethionine which depress protein anabolism, or on diets deficient in essential amino acids. Intravenous tetracycline is said to be particularly dangerous in those with severe malnutrition.

These microvesicular fat diseases have been gathered together using the histological appearances of small droplet fat in the hepatocyte as the criterion for diagnosis. It is realised that not all patients will show every feature described for the group as a whole (Table). The classification has been made in the hope that recognition will encourage research into mechanisms. In particular, in future, it may become possible to identify those at risk of developing such diseases as acute fatty liver of pregnancy, Reye's syndrome, and those reacting abnormally to drugs such as sodium valproate.

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