Co-existence of hepatitis A and adult Reye’s syndrome

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Abstract
Reye’s syndrome is most frequently seen in children but has also been described in adults. This syndrome is usually associated with ingestion of 5-aminosalicylates (ASA) or infection with influenza A, influenza B, or varicella virus. A case of Reye’s syndrome in a 47 year old, previously healthy woman precipitated by ingestion of ASA and acute hepatitis A virus infection is described. Reye’s syndrome was diagnosed on the basis of her clinical course, and the presence of hepatic microvesicular steatosis and characteristic electron microscopic changes in the hepatocyte mitochondria. The diagnosis of hepatitis A was based on higher aminotransferase values than would be expected in Reye’s syndrome alone, viral serology including the presence of hepatitis A IgM and the demonstration of hepatitis A virus RNA on liver biopsy by in situ hybridisation. Mitochondrial injury has been demonstrated in acute hepatitis A which, in addition to ASA, may have precipitated Reye’s syndrome in this patient. The association between hepatitis A and Reye’s syndrome has not been reported before. As hepatitis A virus infection is not sought routinely in patients with Reye’s syndrome, the frequency of this association is unknown.

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Reye’s syndrome is most commonly seen in children and is usually preceded by an upper respiratory tract viral infection. It is an acute, potentially life threatening illness affecting predominantly the brain and liver. We report a case of Reye’s syndrome in a 47 year old adult, which seems to have been precipitated by hepatitis A infection. To our knowledge, this is the first time an association between hepatitis A and Reye’s syndrome has been described.

Case report
A 47 year old female dietitian developed myalgia, rhinitis, and cough. She took acetyl salicylic acid and acetaminophen at the recommended dosage. She subsequently developed nausea and vomiting. Five days after the start of her illness she became stuporous with inappropriate behaviour and was transferred to our institution from her local hospital.

She had been entirely well in the past with previous admission to hospital only for the birth of her four children. Two of her sons suffered from spinal muscular dystrophy. There was no past history of ethanol misuse or liver disease.

On examination, she was afebrile and her blood pressure was 160/90 mm Hg. She was deeply comatose with posturing characterised by pronation and internal rotation of her upper limbs. There was no evidence of papilloedema. Her plantar responses were up, going bilaterally, but there were no other localising neurological signs. She had no stigmata of chronic liver disease and there was no hepatic or splenic enlargement. Preliminary investigation showed the following: white blood cell (WBC) count 6.4 x 10^3/l, haemoglobin 148 g/l, platelet count 248 x 10^3/l, prothrombin time (PT) international normalised ratio (INR) 2.1, partial thromboplastin time 39.6 seconds, aspartate aminotransferase (AST) >5000 IU/l (normal range 5–45 IU/l), alanine aminotransferase (ALT) >5000 IU/l (normal range 5–55 IU/l), alkaline phosphatase 284 IU/l (normal range 40–130 IU/l), lactate dehydrogenase 7602 IU/l (normal range 250–650 IU/l), bilirubin 68 μmol/l (normal range 3–20 μmol/l), albumin 39 g/l (normal range 30–50 g/l), total protein 76 g/l (normal range 60–80 g/l), ammonia 94 mmol/l (normal range 5–80 mmol/l), acetaminophen <10 mg/l, salicylate 31 mg/l (therapeutic level <300 mg/l), serum osmolality 297 mOsm/kg (normal range 280–295 mOsm/kg). Electrolytes and creatinine, ceruloplasmin and copper concentrations were normal. An extensive drug screen was negative. A computed tomography scan of the head showed diffuse cerebral oedema without focal lesions. Lumbar puncture done at admission before liver function tests were available revealed clear fluid with 4 x 10^6 WBC/l, 61 x 10^6 red blood cells per litre, protein 0.47 g/l (normal range 0.15–0.45 g/l), glucose 4.8 mmol/l (normal range 2.2–4.1 mmol/l), blood sugar 7.4 mmol/l (normal range 3.5–9.0 mmol/l). Subsequent viral, bacterial and mycobacterial cultures were all negative. An ultrasound scan of the abdomen revealed homogeneous hepatic parenchyma with patent vessels and no evidence of ascites.
Serological testing by enzyme immunoassay (Abbott Laboratories, Chicago, IL, USA) revealed hepatitis A virus (HAV) specific IgM antibody. Hepatitis B surface antigen, IgM antibody to hepatitis B core antigen, and anti-hepatitis C virus testing was negative.

The patient’s neurological status began to improve on day 4 after admission and by day 8 the endotracheal tube was removed and she was transferred to the ward. The patient was discharged from hospital on day 19 without neurological deficit. Her AST value was 570 IU/l and bilirubin 31 μmol/l one month after discharge. Her liver enzymes were completely normal four months after discharge and she eventually made a complete recovery.

In situ hybridisation for HAV
Infection with HAV was confirmed by using in situ hybridisation. cDNA from two cases, a 22 year old woman with hepatic allograft failure and a 35 year old woman with acute fatty liver of pregnancy, was used as a negative control.

The methods used for in situ hybridisation and riboprobe construction have been described in detail elsewhere.1 The 35S labelled riboprobes were synthesised from plasmid pHAVp16 containing the full length, 7-485 kilobase, p16 HM 175 HAV cDNA cloned into pGEM 3 vector.

Our case had detectable riboprobe signal in the liver to the HAV antisense probe (figs 2A and 2C). This signal to HAV RNA was observed in the hepatic lobules in a scattered and spotty distribution but not overlying the portal triads. No signal was detected after hybridisation to the HAV sense (figs 2B and 2D) or negative control riboprobes (data not shown), demonstrating the specificity of the HAV antisense probe for hybridisation to native HAV RNA. No signal was detected in the negative controls (data not shown).

In order to investigate the possibility of an enzyme deficiency in the mitochondrial β-oxidation cycle, the patient and one of her sons with spinal muscular dystrophy were screened for evidence of defects. While fasting, serum amino acid and plasma lactate concentrations were normal. The patient had a normal total plasma carnitine as well as normal free, acyl and free/total carnitine concentrations. Her son’s acyl carnitine concentration was slightly raised at 39-3 μmol/l (normal range 0–36 μmol/l), but total, free and free/total carnitine concentrations were normal.

Discussion
Reye’s syndrome is most commonly seen in children but has also been reported in adults.3 4 This patient fulfilled the diagnostic criteria for Reye’s syndrome and her liver biopsy specimen showed characteristic microvesicular steatosis and mitochondrial injury. Her lack of neurological deterioration and mild encephalopathy despite deep coma were considered unusual for fulminant hepatic failure and more consistent with Reye’s syndrome. Infection

An electroencephalogram showed diffuse slowing with triphasic waves consistent with severe encephalopathy. When the patient’s liver biochemistry results became available, she was considered to have fulminant hepatic failure secondary to viral hepatitis. The patient was transferred to the intensive care unit where she was intubated and treated with hyperventilation and intravenous mannitol. Percutaneous liver biopsy after two units of fresh frozen plasma revealed diffuse microvesicular steatosis characteristic of Reye’s syndrome (fig 1). The identity of the fat was confirmed by Oil Red O staining of frozen sections and by electron microscopy which also revealed the characteristic rarefaction and structural simplification of mitochondria. Unusual histological findings included a modest portal and peripheral lymphocytic, plasmacytic and eosinophilic inflammatory infiltrate and rare apoptotic bodies within the parenchyma.
with HAV was established with positive IgM serology and by showing the presence of HAV RNA in the liver using in situ hybridisation. Her notably increased AST activity was unusual for Reye’s syndrome. In seven previously reported cases of Reye’s syndrome in adults, the AST activity ranged from 270 to 1500 IU/l.3 The portal and lobular inflammatory cell infiltrate also suggested a second hepatic insult.6

The pathogenesis of Reye’s syndrome is incompletely understood.7 Ultrastructural examination of hepatocytes shows pleomorphic enlarged mitochondria with disrupted cristae, electron lucent matrixes and dense lucent bodies.8 Corkey et al.9 described intrahepatic accumulation of short and medium chain acyl coenzyme A (CoA) intermediates which deplete intramitochondrial ATP. Van Coster et al.10 have shown that although immunologically active enzyme subunits are present in the mitochondrial matrix in normal amounts, there is a non-uniform decrease in mitochondrial enzyme activities. They suggested that a lack of ATP impairs the assembly of enzymes in the intramitochondrial matrix. The resulting compromise in metabolic pathways may be responsible for producing Reye’s syndrome. Moreover, it has been shown that women who are heterozygous for long chain 3-hydroxyacyl CoA dehydrogenase deficiency of the mitochondrial fatty acid β-oxidation cycle may be at risk for severe microvesicular steatosis in the form of acute fatty liver of pregnancy.10

The initial insult that triggers these metabolic abnormalities in Reye’s syndrome is not known. ASA and viruses such as influenza A, influenza B, and varicella have been associated with this syndrome.3,11 Our patient took recommended doses of ASA, but also had an acute infection with HAV as shown by positive acute serology and an inflammatory infiltrate on liver biopsy, which is not a feature of Reye’s syndrome. In addition, positive in situ hybridisation to HAV antisense riboprobe established the presence of HAV RNA within hepatocytes. This association has not been described before and hepatitis A by itself is not known to cause microvesicular steatosis. Furthermore, fulminant hepatic failure owing to hepatitis A alone is an unlikely explanation for deep coma and cerebral oedema in the context of a PT INR of only 2:1. The mechanism by which HAV could induce Reye’s syndrome remains speculative. HAV is found in hepatocytes within intracytoplasmic vesicles.12 It has also been demonstrated in close proximity to damaged mitochondria in cultured African green monkey kidney cells,13 and mitochondrial abnormalities have been identified on ultrastructural studies of chimpanzee livers after inoculation with HAV.14 HAV induced mitochondrial damage together with ingestion of ASA may have induced Reye’s syndrome in our patient. However, mitochondrial damage has not been identified in humans. Alternatively, soluble activated macrophage products induced by viruses may depress mitochondrial respiration.15 Recently, infection with HAV has been identified as a possible immunological trigger for type I autoimmune hepatitis.16,17 An immune mechanism for its role in precipitating Reye’s syndrome is unlikely, however, in view
of the antigen diversity between the various viruses which precede Reye's syndrome and because the primary site of damage is within the mitochondria. Finally, we did not find evidence to suggest a defect in the mitochondrial β-oxidation pathway in the patient or her son with spinal muscular dystrophy; however, such an association is worthy of future study in patients with Reye's syndrome. It is possible that hepatitis A and Reye's syndrome were coincidental findings in this patient, but the simultaneous presentation of two unrelated acute liver diseases seems unlikely. As HAV infection is not routinely sought in patients with Reye's syndrome, the frequency of this association is unknown.

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