Obstetric Medicine
Obstetric Medicine
2017, Vol. 10(4) 186–188

DOI: 10.1177/1753495X17695173
journals.sagepub.com/home/obm
SAGE

Presumed acute fatty liver of pregnancy following influenza A hepatitis

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Abstract

Acute fatty liver of pregnancy is a rare mitochondrial hepatopathy characterised by microvesicular fatty infiltration, and is believed to be due to impaired fatty acid oxidation. Hepatitis following influenza virus infection is uncommon. Rarely influenza virus infection may be complicated by Reye's syndrome, another hepatic microvesicular fat disease. A case of influenza A hepatitis in third trimester of pregnancy, followed by the evelopment of presumed acute fatty liver of pregnancy is described in this report and a potential mechanism why this may have occurred is discussed.

Keywords

Influenza A hepatitis, acute fatty liver of pregnancy, mitochondrial hepatopathy, hepatic fatty acid oxidation, Kupffer cells

Date received: 23 November 2016; accepted: 26 January 2017

Introduction

Influenza virus infection is frequently a more severe illness in pregnant women and is associated with greater morbidity and mortality than in the general population. While elevations of hepatic transaminases are commonly found in the setting of influenza infection in the general population, only a single case of possible influenza hepatitis has been previously described in a pregnant woman. Acute fatty liver of pregnancy (AFLP) is a rare disorder estimated to complicate 5–30 per 100 000 pregnancies. AFLP is a mitochondrial hepatopathy attributed to a defect in mitochondrial beta oxidation and characterised by hepatic microvesicular steatosis. Reye's syndrome and sodium valproate hepatotoxicity also represent microvesicular fat diseases which occur secondary to impaired fatty acid oxidation and share similar clinical features with AFLP. Reye's syndrome may occur as a complication of influenza virus infection, particularly in children. A case of presumed AFLP complicating influenza hepatitis is presented.

Case

A 35-year-old woman, gravida 3 para 2, presented to the emergency department at 33 weeks gestation with a seven day history of fever, dry cough, dyspnoea and arthralgia. Her past history was unremarkable; she was taking no medications other than paracetamol as required and was a non-smoker who drank minimal alcohol. On examination, the patient was afebrile, oxygen saturation was 97% on room air, pulse was 105/min and regular, blood pressure was 120/80 mm Hg and physical examination was otherwise unremarkable. Biochemical testing revealed abnormal liver function tests and mild renal dysfunction (Table 1). The patient was discharged with a provisional diagnosis of a viral illness. At review at antenatal clinic at 34 weeks gestation, it was noted that the patient's symptoms were improving, though she complained of increasing thirst and polyuria. This was attributed to polydipsia of pregnancy. Repeat biochemistry showed improvement in liver function tests but further deterioration in renal function. Review of the investigations from the previous presentation noted a positive nasopharyngeal swab for H1 influenza A by polymerase chain reaction. No further action was taken.

At 37 weeks gestation, the patient's husband found her unconscious. Capillary glucose performed by paramedics was 1.1 mmol/L. Her husband gave a history of ongoing fevers, arthralgia and generalised malaise and one week of vomiting. She had been taking 3–4 g of paracetamol daily. The husband was unaware of the intake of any other medication, herbal or over the counter preparation, or alcohol.

Physical examination revealed a confused, deeply jaundiced woman with temperature of 34.7, SaO_2 of 96% on room air, pulse 120/min and regular and blood pressure was 130/80 mm Hg. Abdomen was soft and non-tender; cardiac and respiratory examination was normal; lower limb reflexes were brisk with ankle clonus. No rash was visible.

Initial investigations demonstrated marked hyperbilirubinaemia, deranged liver function, disseminated intravascular coagulation, acute kidney injury, lactic acidosis and severely depressed antithrombin III (Table 1). Serum sodium was 143 mmol/L (normal 130–148), urine osmolality was 364 mmol/L (normal 238–1044), and urine output was 110 mL/h. Abdominal ultrasound revealed normal liver echogenicity and echotexture and patent portal and hepatic veins. Fetal ultrasound revealed an intrauterine fetal death. The provisional diagnosis was AFLP. The mother was treated with intravenous acyclovir, broad-spectrum antibiotics, N-acetylcysteine and dextrose. The baby was delivered by caesarean section after correction of coagulopathy. Continuous venovenous haemodiafiltration was commenced. Serum paracetamol was 5 mg/L (therapeutic range 10–20); there were no paracetamol metabolites on chromatography, and urine 5 oxo-proline levels were not consistent with paracetamol toxicity. Testing for other causes of viral hepatitis, autoimmune hepatitis, antiphospholipid syndrome, Wilson's disease, alpha-1 antitrypsin and haemochromatosis were negative. Leptospira IgM was equivocal. Serum cortisol was normal. The mother was transferred to a hepatobiliary transplant unit; however, her liver function recovered after a period of 25 days without the need for a liver transplant. Molecular analysis for mutations in hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein) alpha subunit gene on mother and baby was negative. This gene encodes the alpha subunit of the mitochondrial trifunctional protein which catalyses the last three steps of mitochondrial beta-oxidation of long chain fatty acids.

Discussion

Elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were seen in 20%–25% of human subjects

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Table 1. Investigations at different gestations in pregnancy.

	20 weeks	33 weeks	34 weeks	37 weeks	25 days pp
Bilirubin (<20 μmol/L)	5	14	17	214	141
AST (10–45 U/L)	17	408	160	406	279
ALT (5–45 U/L)	13	364	105	146	212
GGT (10–70 U/L)	22	228	206	117	88
ALP (80–250 U/L)	57	298	284	480	123
LD (80–520 U/L)	171			1172	326
Albumin (28–38 g/L)	30	33	29	22	26
Bicarbonate (20–28 mmol/L)	22	17	25	10	25
PT (11–16 s)				>120	13
APTT (23–38 s)				>200	33
Fibrinogen (1.5–4 g/L)				<0.1	4.4
Antithrombin III (80–120%)				1.6%	
Cr (30–70 μmol/L)	49	84	98	265	60
e GFR (> 90 mL/min/1.73 m^2)	> 90	78	65	19	>90
Lactate (0.2–2 mmol/L)				15	
Ammonia (5–35 μmol/L)				56	
Hb (98–137 g/L)	108	140	128	82	94
WBC (5.9–16.9 × 10^9/L)	8.0	11.0	9.8	6.7	14.7
Plts (150–400 × 10^9/L)	223	231	212	62	664
Retics (27–135 × 10^9/L)				83	

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; LD: lactate dehydrogenase; PT: prothrombin time; APTT: activated partial thromboplastin time; Cr: creatinine; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; WBC: white blood cell count; Plts: platelet count; Retics: reticulocyte count; pp: postpartum.

experimentally infected with influenza A or B virus.[1] Rises in hepatic transaminases were not coincident with pyrexia demonstrating that liver damage was not linked to the innate immune response or to virus replication. In a mouse model of primary infection with influenza virus, all animals had elevated ALT and AST peaking after day 8 of exposure. Real time polymerase chain reaction to detect virus genome and inoculation of eggs with tissue samples from acutely infected animals failed to show evidence of viral replication in the liver. On the basis of histological findings, it is postulated that massive expansion of virus specific $CD8^+$ T cells and activation of Kupffer cells in foci of apoptosis leads to release of inflammatory cytokines, hepatic oxidative stress and hepatocyte injury. Recently, it has been demonstrated that infection with PR8 influenza results in Kupffer cells mediating reduced hepatic fatty acid oxidation.[2]

Reye's syndrome, AFLP and sodium valproate hepatotoxicity are thought to occur as a result of impaired mitochondrial oxidation of fatty acids. They share common clinical features and the histologic appearance of hepatic microvesicular steatosis. Reye's syndrome has been reported in adults as well as children following influenza A viral infection.[3] A review of 30 fatal cases of proven influenza A virus infection and encephalopathy noted liver dysfunction in 57% and fatty degeneration was found in 40%.

One previous case of presumed influenza A hepatitis has been reported in pregnancy, though the subject also had prominent itch and elevated bile acids more suggestive of intrahepatic cholestasis of pregnancy.[4] Two cases of AFLP developing postpartum after pregnancy complicated by intrahepatic cholestasis of pregnancy have been reported.[5,6] Shabot et al.[7] described a woman who presented with jaundice, elevated liver function tests, hypoglycaemia, disseminated intravascular coagulation and elevated ammonia levels at 38 weeks gestation. The patient was thought to have AFLP, her condition resolving after delivery. A percutaneous liver biopsy performed on the 10th day postpartum revealed typical features of hepatitis, and hepatitis B surface antigen was positive, illustrating the difficulty in differentiating clinically between acute viral hepatitis and AFLP.

Several potential 'red flags' were missed in this patients care. It is vital to measure prothrombin time as an index of hepatic synthetic function in any pregnant woman with elevated hepatic transaminases. The abnormal renal function at 33 weeks gestation and the significant deterioration one week later mandated further investigation and close observation. Gestational diabetes insipidus is rare complicating 2 to 4 out of 100,000 pregnancies.[8] Vasopressinase, an enzyme produced by placental trophoblasts during pregnancy, degrades arginine vasopressin. The levels of vasopressinase increase 1000-fold between the 7th and 40th weeks of gestation. Vasopressinase is metabolised by the liver, and concentrations may rise in any acute or chronic liver disease resulting in central diabetes insipidus (CDI). While CDI has been described as a rare complication of AFLP, Kennedy et al.[9] described a series of six women presenting in a 2½ year period with CDI complicating AFLP. CDI has also been reported with severe H1N1 influenza illness with a thickened pituitary stalk on magnetic resonance imaging consistent with lymphocytic infundibuloneurohypophysitis.[10,11] It is unclear as to whether the patient presented had diabetes insipidus, though her urine osmolality was relatively low and urine output significant given her depleted intravascular volume on presentation.

In conclusion, a case of influenza hepatitis followed by presumed AFLP is described. The possible mechanism linking these two disease processes is impaired hepatic fatty acid oxidation mediated by the release of cytokines by Kupffer cells during infection with the influenza virus.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

The patient provided written informed consent for publication of the manuscript.

Guarantor

AM.

Contributorship

AM cared for the patient, performed a literature review and wrote the manuscript.

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