Acute fatty liver of pregnancy associated with fetal mitochondrial trifunctional protein deficiency

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Abstract

Acute fatty liver of pregnancy (AFLP) is a devastating disorder of the maternal liver in the third trimester. Recent studies have demonstrated an association between AFLP and fetal fatty acid oxidation disorders. Here, we report a case of AFLP caused by fetal mitochondrial trifunctional protein (TFP) deficiency. A 21-year-old parous woman presented with nausea, genital bleeding and abdominal pain at 33 weeks of gestation. Laboratory data revealed hepatic failure and disseminated intravascular coagulopathy. The patient underwent emergency cesarean section and was diagnosed with AFLP from the clinical characteristics. She was successfully treated with frequent plasma exchange. The newborn presented severe heart failure and died on the 39th day after birth. Tandem mass spectrometry indicated long-chain fatty acid oxidation disorder. Gene analysis demonstrated homozygous mutation in exon 13 of HADHB, the gene responsible for mitochondrial TFP deficiency. The parents carried a heterozygous mutation at the same location in HADHB.

Key words: acute fatty liver of pregnancy, coagulopathy, fatty acid oxidation disorder, gene analysis, mitochondrial trifunctional protein deficiency.

Introduction

Acute fatty liver of pregnancy (AFLP) is a serious condition occurring in the third trimester of pregnancy, with significant perinatal mortality.1 Starting from non-specific manifestations including headache, nausea and fatigue, hepatic dysfunction and coagulopathy progress rapidly, with renal failure and hepatic encephalopathy. Although the etiology of AFLP is still unclear, recent evidence has linked it to an inherited fetal disorder of mitochondrial fatty acid oxidation.1–5 Fatty acid oxidation involves the activities of four enzymes: long-chain acyl-coenzyme A dehydrogenase (VLCAD), long-chain enoyl-coenzyme A hydratase (LCEH), long-chain 3-hydroxyl- coenzyme A dehydrogenase (LCHAD) and long-chain 3-ketoacyl-coenzyme A thiolase (LCKT). Three of them, LCEH, LCHAD and LCKT, are known as trifunctional protein (TFP). TFP deficiency can cause diseases of various degrees of severity which include a form with neonatal onset, a hepatic form with infant onset and a myopathic form with onset in late adolescence. Here, we report a case of AFLP, which was caused by fetal mitochondrial TFP deficiency, diagnosed by gene analysis.

Case Report

A 21-year-old woman (gravida 1, para 1) was referred to Wakayama Medical University Hospital with genital bleeding and abdominal pain at 33 weeks and 4 days of gestation. She bore a healthy baby without any obstetric problems. Prior history and family history were unremarkable, including in terms of inherited disorders. She had pharyngeal pain, nausea and anorexia for
1 week and laboratory tests revealed elevated liver enzymes with hyperbilirubinemia. On admission, the blood pressure was 136/85 mmHg and other vital signs were normal. On vaginal examination, there was a small amount of genital bleeding. Laboratory data revealed alarmingly disturbed liver function: aspartate aminotransferase (AST), 313 IU/L; alanine transaminase (ALT), 454 IU/L; lactate dehydrogenase (LDH), 649 IU/L; total bilirubin, 7 mg/dL; and direct bilirubin, 5.1 mg/dL. Prothrombin time was prolonged to 36.6%, fibrinogen was decreased to 22 mg/dL, antithrombin activity was only 9% and fibrin degradation product was increased to 186.7 μg/dL, demonstrating disseminated intravascular coagulopathy (DIC). Glucose was 89 mg/dL and ammonia was 51 μg/dL. Viral serology tests including hepatitis A, B, C and Epstein–Barr virus were all negative. Her data did not show hemolysis or anemia (hemoglobin, 11.5 g/dL), and the platelet count was relatively low (11.1 × 10⁴/μL).

Fetal ultrasonography showed cardiac dilation and the cardiothoracic area ratio was 40%. Estimated fetal body weight was 1802 g (−1.1 standard deviations [SD]). There was no evidence of retroplacental hematoma. A cardiotocogram showed a normal baseline with decreasing variability and some late decelerations.

In view of the severe liver dysfunction, maternal DIC and non-reassuring fetal status, emergency cesarean delivery was performed after fresh frozen plasma (FFP) and fibrinogen transfusion. The mother and the baby were admitted to the intensive care unit and the neonatal intensive care unit, respectively. On the 2nd day after delivery, the mother was somnolent because of severe hypoglycemia. Results of abdominal ultrasound and computed tomography scans demonstrated her fatty liver. Combined with laboratory findings such as liver failure and severe coagulopathy, as well as the clinical features, she was diagnosed with AFLP, which fulfilled the Swansea criteria. Frequent plasma exchange and transfusion of platelets and FFP led to gradual recovery of her general condition (Fig. 1).

Liver biopsy was performed on the 58th day. Pathologic examination showed hepatocyte dropout, cholestasis and portal fibrosis, lacking microvesicular steatosis, which is a typical finding of AFLP. She was discharged on the 60th day after cesarean delivery.

The newborn was a female with a birthweight of 1659 g (−1.2 SD). Apgar scores were 9 and 9 at 1 and 5 min, respectively. The baby showed severe metabolic acidosis, while the liver function was within the normal range: lactic acid, 140.8 mg/dL; AST, 26 IU/L; ALT, 9 IU/L; LDH, 355 IU/L; total bilirubin, 1.7 mg/dL; and direct bilirubin, 0.3 mg/dL. The baby had severe heart failure. Despite intensive therapy, the baby died of cardiomyopathy on the 39th day after birth. Tandem mass spectrometry revealed that C16-OH and C18:1-OH were increased to 1.42 and 2.17 nmol/mL, respectively, indicating long-chain fatty acid oxidation disorder. In order to clarify the inherited disorder associated with fatty acid oxidation, gene analysis was performed on skin fibroblasts obtained from the baby and on blood samples from the parents, after acquiring informed consent. Gene analysis of the baby demonstrated homozygosity of 1136A>G, PH379R, in exon 13 of HADHB, the gene responsible for mitochondrial TFP deficiency. The parents carried a heterozygous mutation at the same location in HADHB. We did not perform gene analysis on the parents’ first baby because this baby was 2 years old and could not consent to genetic examination. The parents’ first baby had undergone acylcarnitine profile analysis, showing normal results. We provided genetic counseling for the parents about subsequent pregnancies including pre-implantation genetic diagnosis.

**Discussion**

Acute fatty liver of pregnancy is a rare liver disorder with an incidence of 1/13000 deliveries, and has significant perinatal morbidity and mortality. Clinically, non-specific manifestations including abdominal pain, nausea/vomiting and fatigue are presented for 1 or
2 weeks at an early stage. It is common that women with AFLP exhibit elevated liver enzymes and bilirubin, elevated ammonia, hypoglycemia, coagulopathy, acute renal failure and hepatic encephalopathy. Pregnant women with AFLP and their fetuses are at risk of death even if they are delivered quickly.

Histologically, AFLP is characterized by microvesicular hepatic steatosis, while widespread necrosis or inflammation is absent. Although liver biopsy is needed to make a definitive diagnosis of AFLP, it is seldom performed considering the complications in the presence of coagulopathy and hepatic dysfunction. In our case, there were no typical histological characteristics of AFLP in specimens of liver biopsy performed on the 58th day, possibly because the subject’s liver tissues had recovered. Our case was diagnosed as AFLP from the clinical features, including imaging and laboratory findings based on the Swansea criteria.

Despite manifestations of the clinical features of AFLP, its pathogenesis remains to be clarified, and until recently, it has been considered a mysterious disorder. Recent evidence has demonstrated that AFLP is associated with a fetal disorder of mitochondrial fatty acid oxidation. Mitochondrial β-oxidation of fatty acids is a complex process that consists of four enzymatic reactions resulting in the sequential removal of two-carbon, acetyl-coenzyme A units (Fig. 2). One of the mitochondrial enzymes, TFP, is a hetero-octamer of four α- and β-subunits and catalyzes the last three reactions of the mitochondrial fatty acid β-oxidation spiral with longer chain substrates. The α-subunit has LCEH and LCHAD activities, while the β-subunit has LCKT activity (Fig. 2). The genes that encode the α- and β-subunits are HADHA and HADHB, respectively.

Trifunctional protein deficiency is classified into two different biochemical phenotypes: one represents the existence of both subunits and the lack of only LCHAD activity, and the other represents the absence of both subunits and the lack of all three TFP activities, although their clinical features are similar. LCHAD defect is usually caused by the common 1528G>C transversion in HADHA in Caucasians, and over 60 cases have been described to date. More than 50 cases of TFP deficiency have been reported and 26 of them showed mutations of HADHB. In Japan, nine cases of TFP deficiency with mutations of HADHB were reported until now, whereas LCHAD defect characterized by HADHA mutations were not reported. Inheritance of TFP defects occurs in an autosomal recessive manner, which means affected individuals must have two mutated alleles of the TFP gene for which the enzymatic activities of their products are impaired and both parents are heterozygous carriers.

In 1991, Schoeman et al. first reported the association between recurrent AFLP cases and LCHAD defect, suggesting that affected women may have an inherited enzyme deficiency in β-oxidation, predisposing them to AFLP. Chakrapani et al. reported the association of maternal liver disease and complete TFP deficiency in four cases. In the present study, homozygous mutation of HADHB, which is the gene responsible for TFP deficiency, was found in a newborn baby. The parents showed heterozygosity at the same location in HADHB. Purevsuren et al. reported compound heterozygous mutations of HADHB, one of which was the same as ours. Their transient expression analysis of mutant cDNA revealed that the enzyme activity of the mutated TFP was extremely reduced.

It is hypothesized that unmetabolized free fatty acids return to the mother’s circulation via the placenta in cases in which the fetal enzyme activity of TFP is extremely impaired. Toxic metabolites strain maternal hepatic activity and overwhelm any diminished maternal hepatic enzyme activity, resulting in the symptoms of AFLP (Fig. 3). Environmental stress including a high-fat diet may lead to the further accumulation of toxic metabolites in the genetically susceptible mother. In terms of fetal pathophysiology, intraterine
cardiomyopathy caused by severe cardiac mitochondrial proliferation in TFP deficiency may lead to lethality.12

In summary, AFLP is a serious maternal disorder occurring in the third trimester of pregnancy with significant perinatal mortality. Recent evidence demonstrates that fetal fatty acid oxidative disorders are one of the mechanisms underlying the pathophysiology of AFLP. Early detection and treatment are essential for better prognosis for both mother and newborn. Genetic counseling should be provided to the parents in subsequent pregnancies including pre-implantation genetic diagnosis.

Disclosure
The authors have no conflict of interest.

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